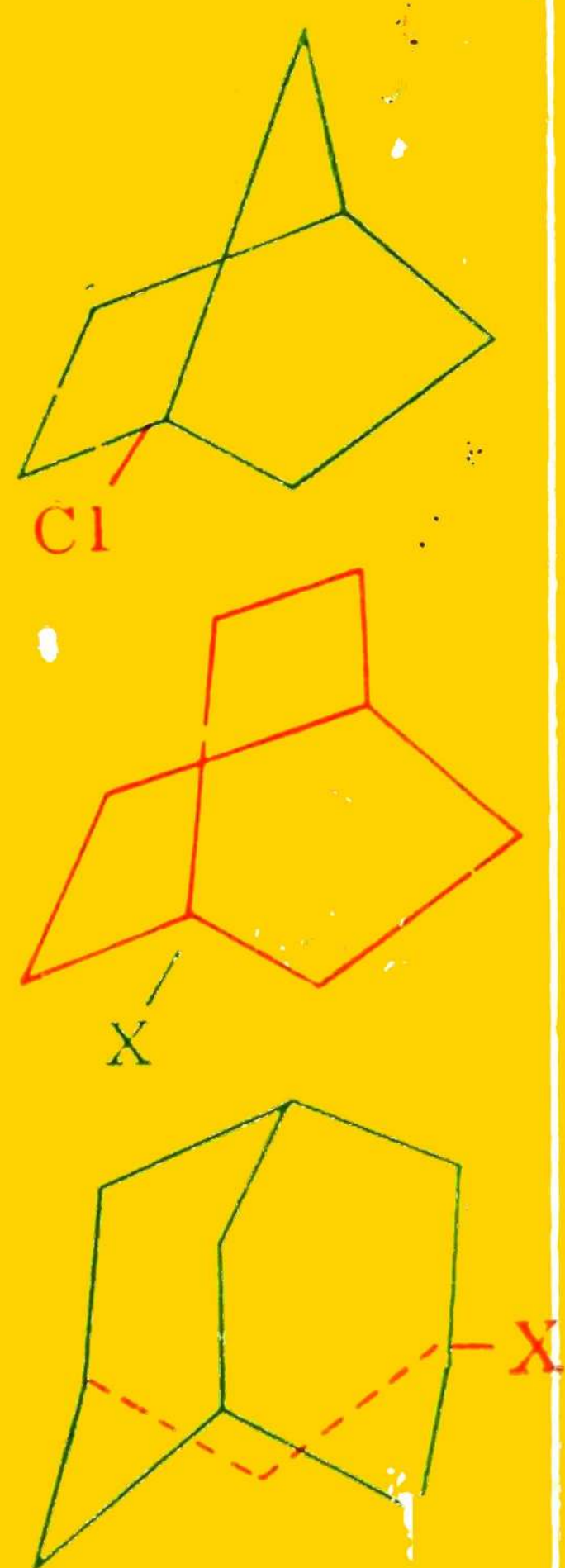
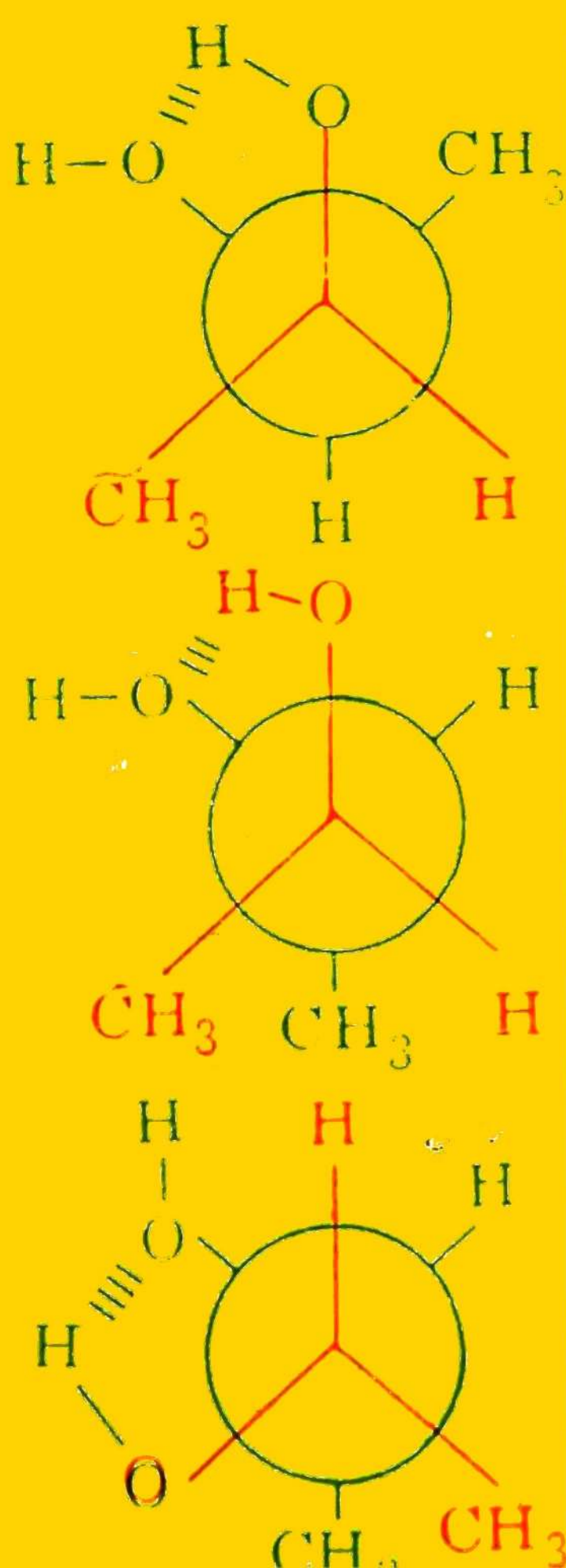
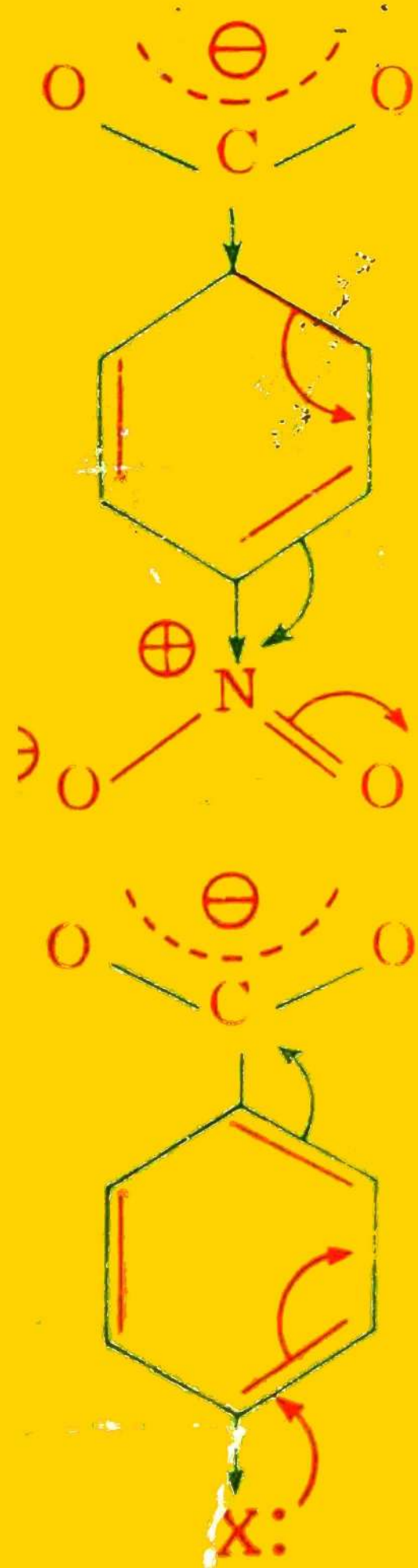


Problems and Exercises in Organic Chemistry

MIR

PUBLISHERS

MOSCOW



Problems and Exercises in Organic Chemistry

The book presents problems and exercises in organic chemistry under the following headings: the nomenclature of organic compounds; free-radical reactions; reactions of nucleophilic substitution in the aliphatic series; oxidation-reduction reactions; condensation reactions and the tautomerism of carbonyl compounds; organomagnesium synthesis; electrophilic and nucleophilic substitution reactions in the aromatic amines and diazo compounds; carbocycles and heterocycles. Considerable attention is paid to problems and exercises based on the present-day theory of organic reactions. Each chapter is supplied with a brief introduction; answers are given to the most sophisticated problems.



А. Е. Агрономов, И. Г. Болесов,
В. М. Потапов, В. Л. Фосс, С. С. Чуранов,
Ю. С. Шабаров

Задачи
и упражнения
по органической
химии

Издательство Московского Университета

PROBLEMS AND EXERCISES IN ORGANIC CHEMISTRY

CONTRIBUTING AUTHORS:

A. E. Agronomov, I. G. Bolesov,
V. M. Potapov, V. L. Foss, S. S. Churanov,
Yu. S. Shabarov

Translated from the Russian
by Artavaz Beknazarov

Mir Publishers • Moscow

First published 1974

Second printing 1977

На английском языке

© English translation, Mir Publishers, 1974

CONTENTS

Preface	7
Chapter 1. Nomenclature of Organic Compounds	9
1. Trivial, Rational and Systematic Names	11
2. Compounds of Acyclic Structure	14
3. Carbocyclic Compounds	27
4. Heterocycles	33
5. Some Problems of the Practical Application of Organic Nomenclature	34
6. Material for Exercises	38
Chapter 2. Free-Radical Reactions	60
Introduction	60
Problems and Exercises	61
Answers	63
Chapter 3. Nucleophilic Substitution in the Aliphatic Series . .	66
Introduction	66
Problems and Exercises	70
1. Strength of Acids and Bases. Nucleophilicity	70
2. Reaction Mechanisms, Selection of Optimal Reaction Conditions, Reactivity	73
3. The Use of Nucleophilic Substitution Reactions for Synthetic Purposes	81
Answers	85
Chapter 4. Condensation Reactions and Tautomerism of Carbonyl Compounds	120
Introduction	120
Problems and Exercises	125
1. General Properties of Carbonyl Compounds. Tauto- merism	125
2. Condensations of the Aldol and Croton Type	129
3. Ester Condensation and Related Reactions	131
4. Syntheses with Acetoacetic and Malonic Esters	132
5. Reactions of Carbonyl Compounds	133
Answers	137

Chapter 5. Oxidation and Reduction	160
Introduction	160
Problems and Exercises	168
1. General Questions	168
2. Reduction	169
3. Oxidation	172
4. Combination Problems	178
5. Structure Determination	180
Answers	183
Chapter 6. Organomagnesium Compounds	190
Problems and Exercises	190
1. Preparation and Structure of Organomagnesium Com- pounds	190
2. Reactivity of Organomagnesium Compounds	193
3. Application of Organomagnesium Compounds for Syn- thetic Purposes	204
Answers	210
Chapter 7. Substitution Reactions in the Aromatic Nucleus	244
Problems and Exercises	245
1. General Concepts of Electrophilic Substitution	245
2. Orientation in Electrophilic Substitution. Relative Reactivity of Aromatic Compounds and Methods of Generation of Electrophilic Reagents	247
3. Use of Electrophilic Substitution Reactions for Syn- thetic Purposes	250
4. Nucleophilic Substitution Reactions	253
5. Some Properties of Phenols, Aromatic Acids and Amines	254
Answers	255
Chapter 8. Aromatic Amines and Diazonium Compounds	267
Problems and Exercises	270
1. Reduction of the Nitro Group Attached to the Aroma- tic Nucleus	270
2. Preparation of Diazo Compounds	274
3. Stability and Structure of Diazo Compounds	275
4. Substitution Reactions of the Diazo Group	276
5. Azo Coupling Reactions	278
6. Use of Diazo Compounds for Preparative Purposes	282
Answers	285
Chapter 9. Synthesis and Properties of Heterocyclic Compounds	308
Introduction	308
Problems and Exercises	309
1. General Properties and Reactions of Heterocycles . .	309
2. Syntheses of Heterocyclic Compounds and Their Con- versions	313
Answers	317

PREFACE

In studying organic chemistry great importance is attached to problems and exercises which are discussed at seminars or worked up individually by the student. Problems and exercises aid in acquiring a deeper, creative mastery of the material and stimulate the home study of the student.

By tradition, books of problems and exercises are largely devoted to synthetic organic chemistry. At present, however, there is an urgent need for problems and exercises of a new type composed with account of the present-day theory of organic reactions. It is problems of this type that are presented in this collection. The book provides answers and solutions to the most important and complicated problems and exercises.

The authors consider it useful to present most of the answers in the form of supporting discussion containing no formulas and reaction equations. Giving the required orientation, such answers however contain no direct prompting. Fundamental theoretical questions are naturally not discussed in a full measure. The purpose of the explanations is to guide the student's thought in a proper direction and to remind him of the theory material that can help to get the correct answer. In some cases references are given to textbooks and monographs in organic chemistry.

The detailed consideration of the nomenclature of organic compounds in Chapter 1 is thought of as necessary because no complete textbook of nomenclature is available for the student to master the general principles and basic rules of modern chemical nomenclature.

CHAPTER 1

NOMENCLATURE OF ORGANIC COMPOUNDS

Mastery of the scientific terminology is a first and indispensable step in the study of any science. The most important part of the chemist's parlance is the exact names of chemical compounds. To assign an exact name to an inorganic substance it is sufficient, as a rule, to indicate the composition of its molecule. In organic chemistry, however, because of the widespread phenomenon of isomerism, this is not sufficient: a completely unambiguous name of an organic compound must reflect its structural formula.

The nomenclature of organic compounds must make it possible to pass from the structural formula of a compound to its name and back again—to construct the structural formula by the name. For this purpose there are compound word-names built of the designations of simpler constituent parts and numbers or letters (so-called locants) characterizing the position of component parts. A structural formula can be described in words in different ways and there exist and are used simultaneously several systems of organic nomenclature; an organic compound, more or less complicated, may have several different names attached to it.

What could be simpler, one would think, as to work out a unified system of nomenclature covering all organic compounds, a nomenclature to be used by all chemists! A nomenclature, however, is part of the language. Just as there exist word-synonyms, so there are also synonyms in the nomenclature of organic compounds and to fight against them is tantamount to battle the windmills. To introduce a new nomenclature and bury the old one in oblivion would be pointless for the simple reason that all the old literature would become obscure.

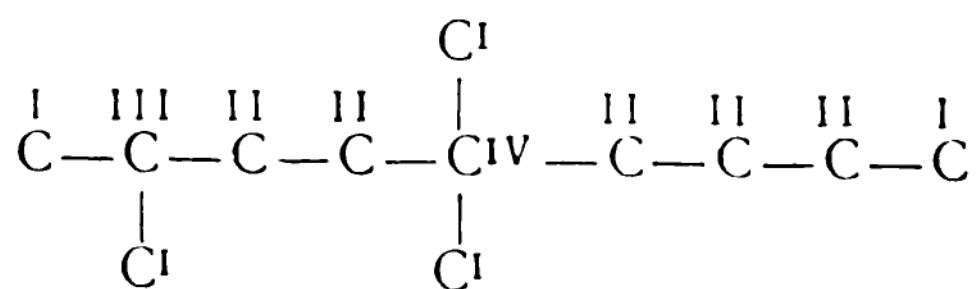
The existence of different systems of nomenclature and the multiplicity of the names of organic compounds create additional difficulties in studying organic chemistry. At the same time these difficulties are reduced noticeably if, at the very outset, certain principles common to all the currently used systems of nomenclature are well ascertained.

Thus, in particular, in building names of complex organic compounds, wide use is made of the names of saturated hydrocarbons (alkanes) and of the corresponding univalent radicals (alkyls).

The first four paraffinic hydrocarbons with an unbranched chain have trivial (common, nonsystematic) names and the others have Greek numerals as their roots and the ending *-ane*. The names of radicals formed when one hydrogen atom is subtracted from the terminal carbon atom of unbranched saturated hydrocarbons are built up of the names of corresponding hydrocarbons with the ending *-ane* being replaced by *-yl* (Table 1).

Branched radicals of the formula $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH}-(\text{CH}_2)_n- \\ \diagdown \\ \text{CH}_3 \end{array}$ are prefixed with *iso-*: $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH}- \\ \diagdown \\ \text{CH}_3 \end{array}$ is isopropyl; $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH}-\text{CH}_2- \\ \diagdown \\ \text{CH}_3 \end{array}$ is isobutyl; $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH}-(\text{CH}_2)_4- \\ \diagdown \\ \text{CH}_3 \end{array}$ is isoheptyl, etc. It is incorrect to use the prefix *iso-* for radicals having no "isopropyl fork" at its end. For example, $\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ \text{CH}- \\ \diagdown \\ \text{CH}_3 \end{array}$ is a secondary butyl, not an isobutyl.

Use is also made of the well-known concept of primary, secondary, tertiary and quaternary carbon atoms. These designations specify how many valencies a particular carbon atom loses to be attached to other carbon atoms: primary stands for one, secondary for two, tertiary for three, and quaternary for four:



Names of Alkanes and Alkyls

TABLE 1

Alkanes		Alkyls	
formula	name	formula	name
CH_4	Methane	CH_3-	Methyl
C_2H_6	Ethane	CH_3-CH_2-	Ethyl
C_3H_8	Propane	$\text{CH}_3-(\text{CH}_2)_2-$	Propyl
C_4H_{10}	Butane	$\text{CH}_3-(\text{CH}_2)_3-$	Butyl
C_5H_{12}	Pentane	$\text{CH}_3-(\text{CH}_2)_4-$	Pentyl (amyl)
C_6H_{14}	Hexane	$\text{CH}_3-(\text{CH}_2)_5-$	Hexyl
C_7H_{16}	Heptane	$\text{CH}_3-(\text{CH}_2)_6-$	Heptyl
C_8H_{18}	Octane	$\text{CH}_3-(\text{CH}_2)_7-$	Octyl
C_9H_{20}	Nonane	$\text{CH}_3-(\text{CH}_2)_8-$	Nonyl
$\text{C}_{10}\text{H}_{22}$	Decane	$\text{CH}_3-(\text{CH}_2)_9-$	Decyl
$\text{C}_{11}\text{H}_{24}$	Undecane	$\text{CH}_3-(\text{CH}_2)_{10}-$	Undecyl
$\text{C}_{32}\text{H}_{66}$	Dotriacontane	$\text{CH}_3-(\text{CH}_2)_{31}-$	Dotriacontyl

It is obvious that primary carbon atoms can reside only at the ends of a carbon chain, secondary ones—inside the chain (or cycle), tertiary and quaternary at sites of branching.

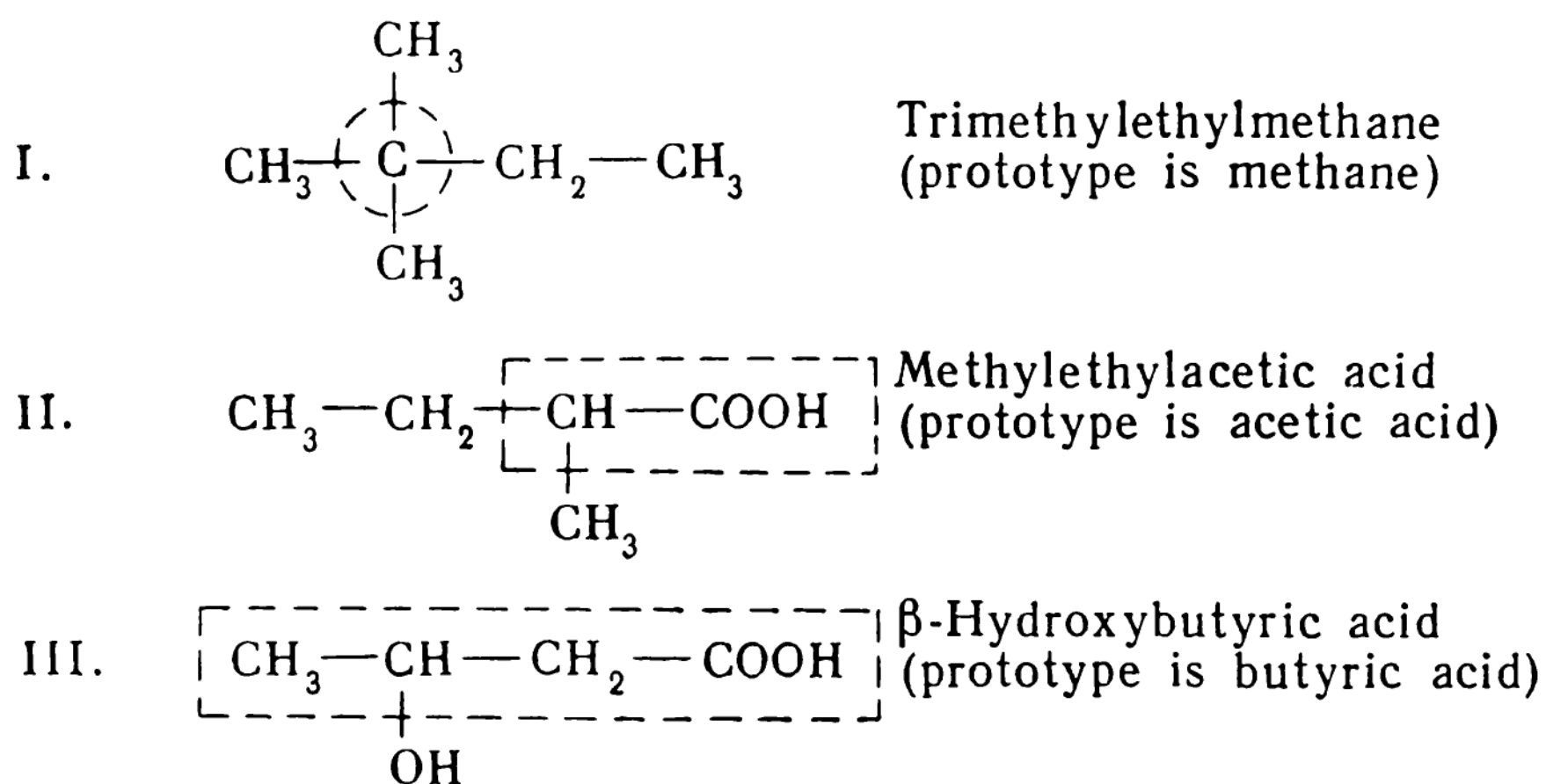
1. TRIVIAL, RATIONAL AND SYSTEMATIC NAMES

In the initial period of the development of organic chemistry when the conceptions of the nature of organic substances were rather obscure, these substances were given *common*, or *trivial*, names. The origin of such names is often associated with natural sources from which these compounds were derived (pivalic acid, butyric acid, urea, lactic acid, vanillin), with the most characteristic properties (indigo, cacodyl, fulminic acid), or with the method of preparation (sulphuric ether, pyrrolic acid). Certain compounds were named after scientists who investigated them (Michler's ketone, Grignard reagent).

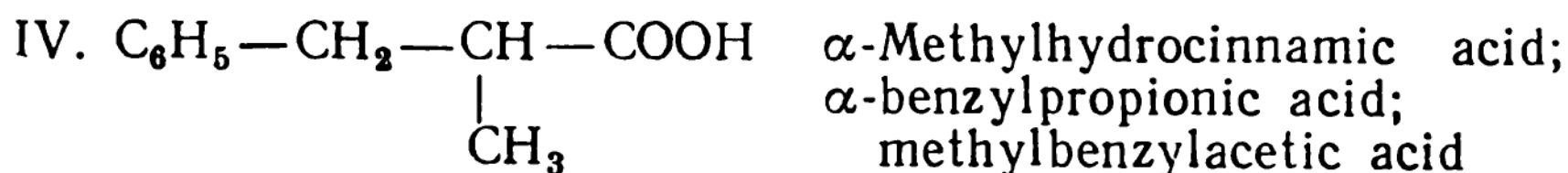
Trivial names do not provide information on the chemical nature of compounds and do not decipher their structures. Such names burden the memory and make it difficult to assimilate the factual material. For widely used compounds they are more convenient than *structural* or *systematic*.

matic names, i.e., names which reflect the molecular structure of organic compounds.

Historically, the first type of systematic names—*rational* names (*semisystematic* or *semitrivial* names)—is the nomenclature expression of the theory of types prevailing in organic chemistry in the forties and fifties of the last century. Such names convey sufficiently clearly the structure of not too complex organic compounds through comparison of the structure of a given substance with that of its prototype taken as a basis for naming it. Rational names are still used at present. How they are constructed will be clear from the following examples:



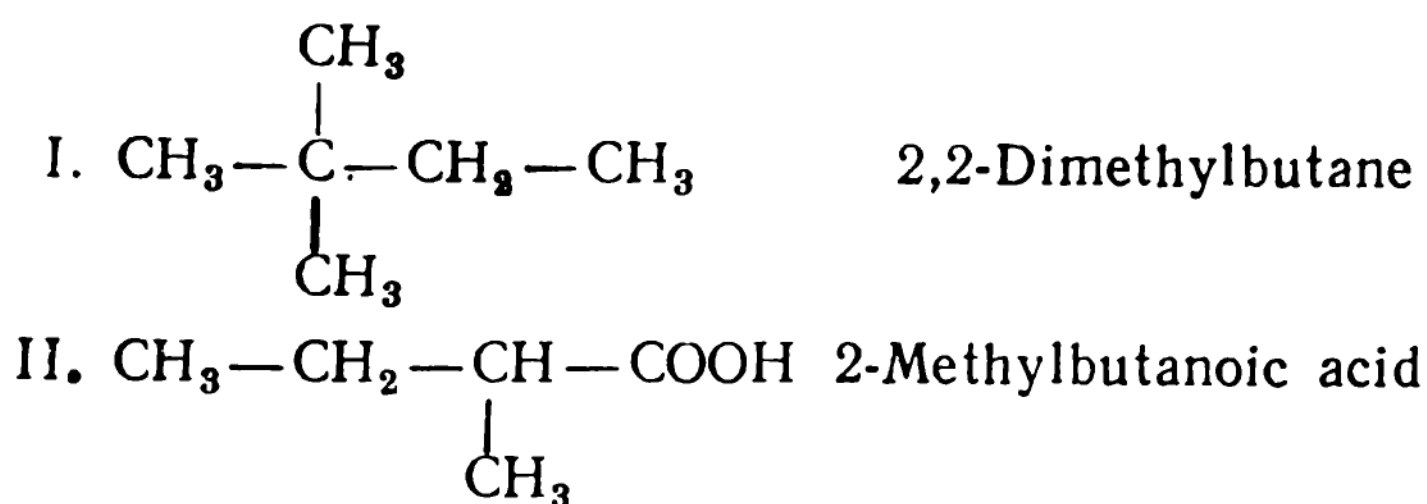
It is important to emphasize that current rational nomenclature makes use, as prototypes, not only of the simplest members of the homologous series (methane in example I, and acetic acid in example II), but also of more complex compounds (examples III and IV). This imparts more flexibility and expressiveness to rational names but at the same time gives rise to various rational names for a compound. For example,



The principles of rational nomenclature are also used in regional nomenclatures devised specifically for certain comparatively narrow branches of organic chemistry (terpenes, steroids).

In 1892, the International Congress at Geneva accepted a nomenclature, the theoretical foundation of which was the theory of chemical structure. Geneva names express in a straightforward way the structure without resorting (as is the case in rational nomenclature) to a comparison of the compound being named with the simpler prototype. Geneva names describe the carbon skeleton of an organic compound and indicate the nature, number and position of the substituents contained in this skeleton. The designation of the carbon skeleton serves as a basis for the name of a compound, the presence of multiple bonds and substituents being reflected in prefixes and suffixes. With this approach any organic compound is found to be a substituted hydrocarbon: this type of nomenclature may be called *substitutive*.

For instance, the structures I and II given above will have the following names:



An attempt was made at Geneva to create a strictly unique nomenclature (one official name being assigned to each compound), but this was actually achieved for relatively simple organic compounds.

New rules concerning the nomenclature of organic compounds were approved at Liege in 1930. The Liege nomenclature is also substitutive but, in contrast to the Geneva nomenclature, it declares the "flexibility" principle—the rightfulness of the existence of several names for a compound. Outwardly, Liege names are like Geneva ones. Both systems are used at present.

In 1947, a new Commission on Nomenclature was appointed by the International Union of Pure and Applied Chemistry (IUPAC) for further work on the nomenclature of organic compounds. The work of the Commission was guided by the principle of ordering (codifying) existing names; only obviously erroneous names were rejected. The IUPAC

rules, like those approved at Liege, are not aimed at achieving the uniqueness of names and creating a unified system for naming compounds.

Though the IUPAC nomenclature has not yet been worked out completely, even now it constitutes a book which has about 300 pages with hundreds of rules. For comparison, the Liege nomenclature consisted of 68 rules on 12 pages, and the Geneva one, of 62 rules on 10 pages. The great number of the IUPAC rules is due in part to the increase in the variety and number of known organic compounds, but it arose primarily from the desire of the authors to "codify" the existing practice in all its variety.

Thus, the IUPAC rules are a sort of collection of chemical "folklore"—the live language spoken by chemists. These rules generalize the nomenclature practice of the entire century and, with all its shortcomings, constitute the most complete collection of various currently used correct names of organic compounds.¹

We will consider below the names used in different systems of nomenclature for various classes of organic compounds.

2. COMPOUNDS OF ACYCLIC STRUCTURE

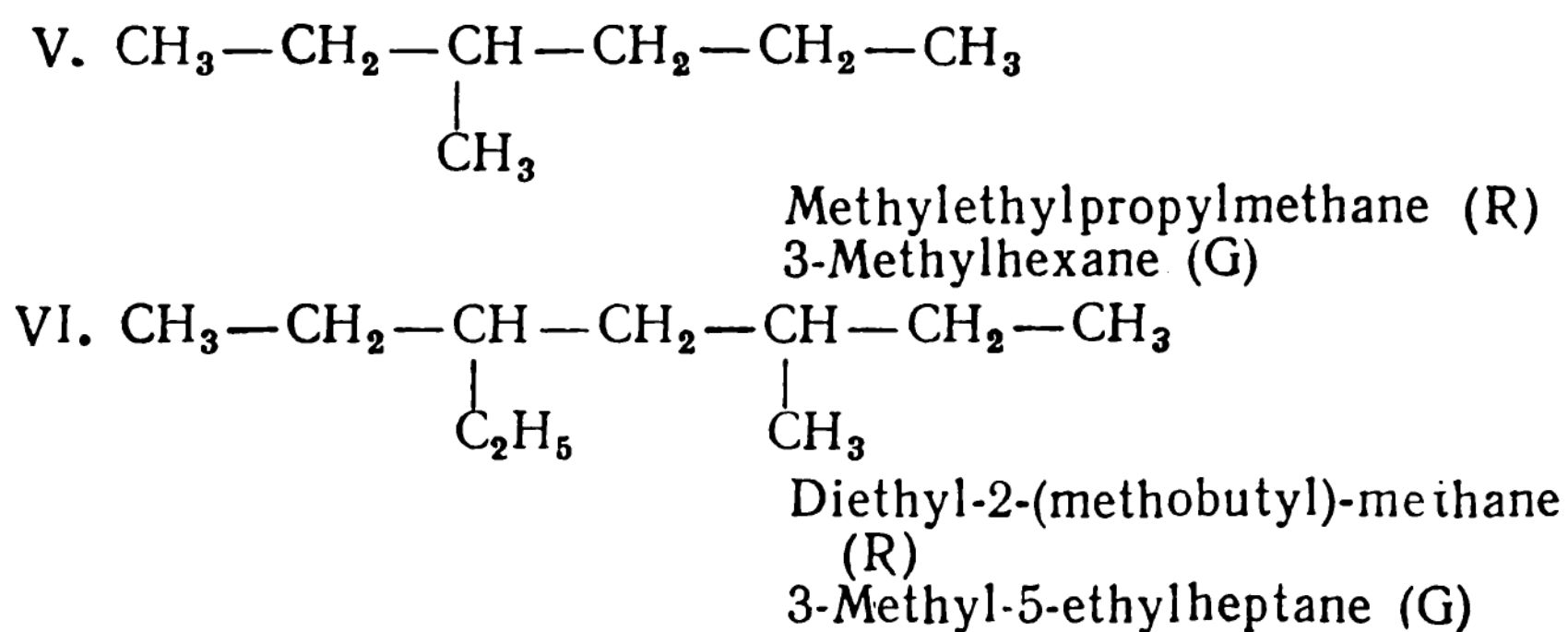
THE NOMENCLATURE OF PARAFFINIC HYDROCARBONS

According to *rational nomenclature*, paraffinic hydrocarbons are usually named as derivatives of methane. This method of naming compounds is clear from example I; some more complicated examples will be discussed below.

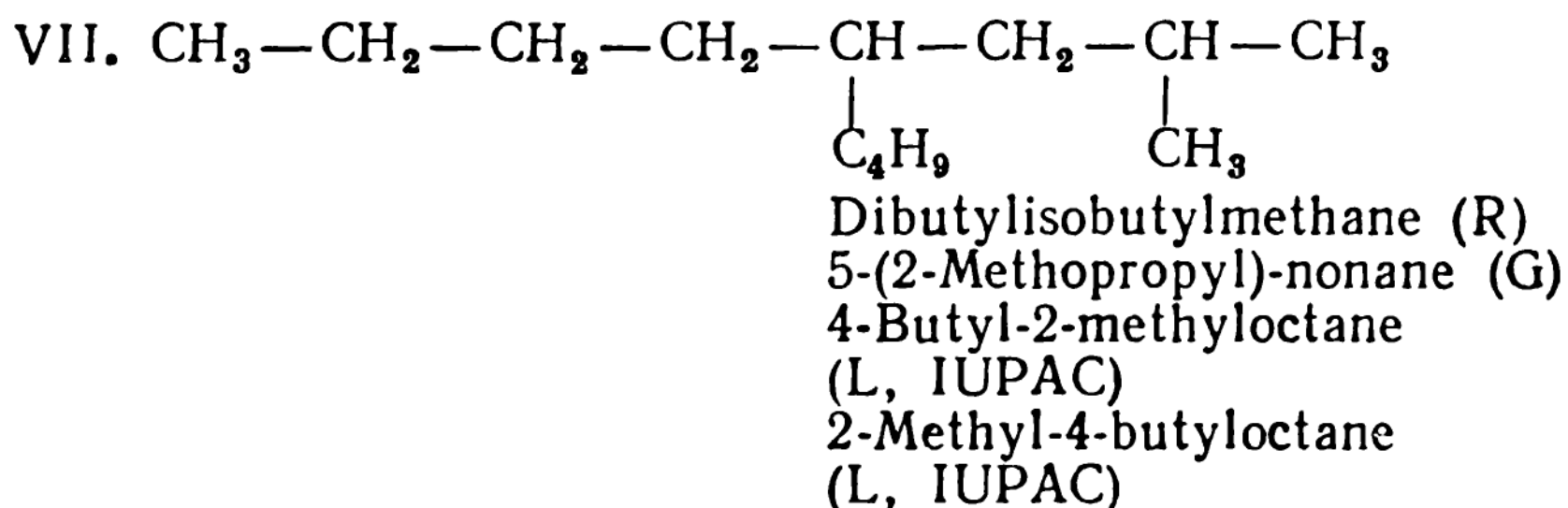
According to the *Geneva nomenclature*, in the structural formula of a paraffinic hydrocarbon one must first look for

¹ Two comprehensive sets of rules have been published which cover much—indeed most—of organic chemistry: (1) *IUPAC Nomenclature of Organic Chemistry*, 1957, *Section A*. Hydrocarbons, *Section B*. Fundamental Heterocyclic Systems. Butterworths, London, 2nd ed., 1966. (2) *IUPAC Nomenclature of Organic Chemistry*, 1965. *Section C*. Characteristic Groups Containing Carbon, Hydrogen, Oxygen, Nitrogen, Halogen, Sulfur, Selenium, and/or Tellurium, Butterworths, London, 1965. For details see R. S. Cahn, *An Introduction to Chemical Nomenclature*, 3rd ed., Butterworths, London, 1968 and *Handbook for Chemical Society Authors*, Special Publication No. 14, The Chemical Society, Burlington House, London, W. 1.—*Tr.*

the longest chain of carbon atoms (if there are several such chains in the structure, choose the chain with the largest number of branchings). This chain constitutes the stem of the name; the omitted parts of the carbon skeleton (side chains) are regarded as substituents into the main chain: their names are written as designations of radicals before the name of the main chain with indication of the number of a carbon atom (locant), at which the side chain stands. Numbering is carried out from the end of the chain which is closest to the side chain (example V), and if there are several side chains, the simplest one is chosen (example VI) ¹:



According to the *Liege rules* and *IUPAC nomenclature* the choice of the main chain for paraffinic hydrocarbons and its numbering is done in the same way as prescribed by the Geneva rules. In IUPAC nomenclature, however, what is given a more detailed consideration is the rules for deciding the seniority of radicals. The only difference is that according to the Liege rules and IUPAC rules one is permitted to enumerate radicals in a name not only in order of increasing complexity but also in alphabetical order (meaning in different ways in different languages). For example,



¹ Here and further in the text R stands for rational names, G for Geneva names, and L for Liege names.

If a hydrocarbon has a strongly branched structure, it may become necessary to designate the branchings of the second and higher orders. One of the methods used for this purpose is to use the names of certain branched radicals in prefixes (Table 2). Another way was suggested in the Geneva rules: to designate second-order branchings with the prefixes *metho-*, *etho-*, *propo-*, etc. This method however did not receive wide recognition, though it was formally approved in the Liege rules.

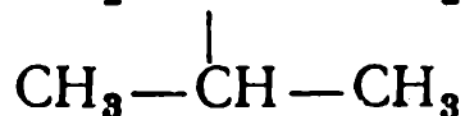
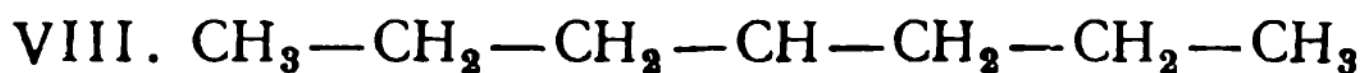
In IUPAC rules, for branched radicals containing up to four carbon atoms (and also important radicals with five carbon atoms—see Table 2), it is recommended to make use of their rational names (examples VIII-IX). And if it becomes necessary to name a more complex side chain, it is then regarded as an independent system (with its “main chain”, starting from the site of junction with the main chain of the designated hydrocarbon, and with its branchings), the

TABLE 2

Names of Some Alkyls

Formula of radical	Names		
	Rational	Geneva, Liege	IUPAC
$\begin{array}{c} \text{CH}_3-\text{CH}_2-\text{CH}_2- \\ \\ \text{CH}_3-\text{CH}-\text{CH}_3 \end{array}$	Propyl Isopropyl	Propyl Methoethyl	Propyl Isopropyl
$\begin{array}{c} \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2- \\ \\ \text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}_3 \end{array}$	Butyl <i>sec</i> -Butyl	Butyl 1-Methopropyl	Butyl <i>sec</i> -Butyl
$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH}-\text{CH}_2- \end{array}$	Isobutyl	2-Methopropyl	Isobutyl
$\begin{array}{c} \text{CH}_3 \\ \\ (\text{CH}_3)_3\text{C}- \end{array}$	<i>tert</i> -Butyl	Dimethoethyl	<i>tert</i> -Butyl
$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH}-\text{CH}_2-\text{CH}_2- \end{array}$	Isoamyl	3-Methobutyl	Isopentyl
$\begin{array}{c} \text{CH}_3 \\ \\ (\text{CH}_3)_3\text{C}-\text{CH}_2- \end{array}$	—	2,2-Dimetho- propyl	Neopentyl

suffix *-yl* is added to the resulting name, and the name of the complex radical is placed (if necessary, in parentheses), as usual, before the name of the main chain (example X).



Dipropylisopropylmethane (R)

4-Methoethylheptane (G, L)

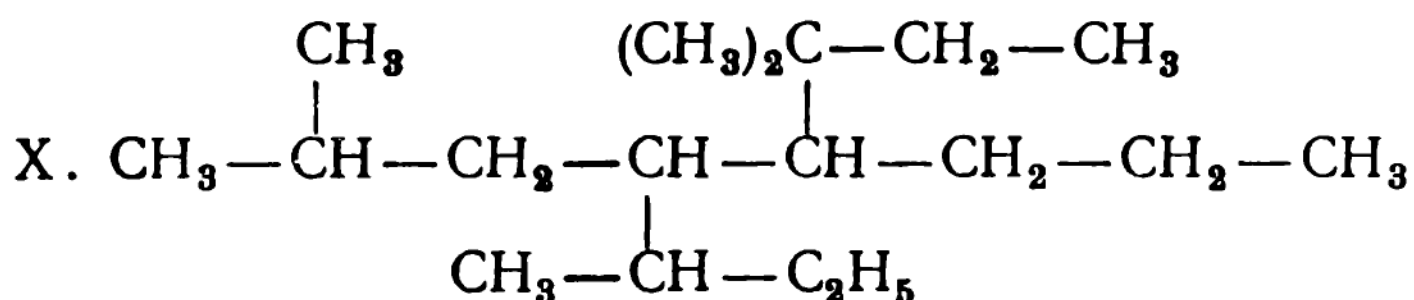
4-Isopropylheptane (IUPAC)



Butyl-*tert*-butylisoamylmethane (R)

2-Methyl-5-(1,1-dimethoethyl)-nonane (G)

2-Methyl-5-*tert*-butylnonane (IUPAC)



Isobutyl-*sec*-butyl [1-(1,1-dimethopropyl)-butyl]-methane (R)

2-Methyl-4-(1-methopropyl)-5-(1,1-dimethopropyl)-octane (G)

2-Methyl-4-*sec*-butyl-5-(1,1-dimethylpropyl)-octane (IUPAC)

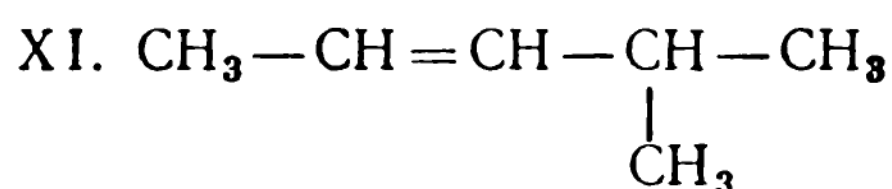
NOMENCLATURE OF UNSATURATED HYDROCARBONS

According to rational nomenclature, hydrocarbons with one double bond are named as derivatives of ethylene (example XI), and those with a triple bond, as derivatives of acetylene (example XII). For more complex hydrocarbons use may be made of other prototypes as the stem of names.

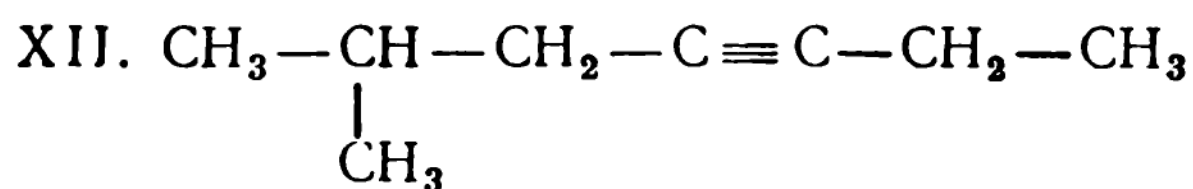
According to the Geneva nomenclature, the presence of a double carbon-carbon bond is expressed by replacing the final *-ane* by *-ene*; that of a triple bond by replacing the final *-ane* by *-yne*; alkenes that contain two double bonds are called dienes and those containing three double bonds, trienes, etc. The position of multiple bonds is indicated by the numbers of atoms from which these bonds originate. The

choice of the main chain and its numbering are not affected by the presence of multiple bonds according to the Geneva rules. This reflects one of the basic principles of the Geneva nomenclature (Sec. 17)—the numbering of hydrocarbons is retained for the substitution products of hydrocarbons.

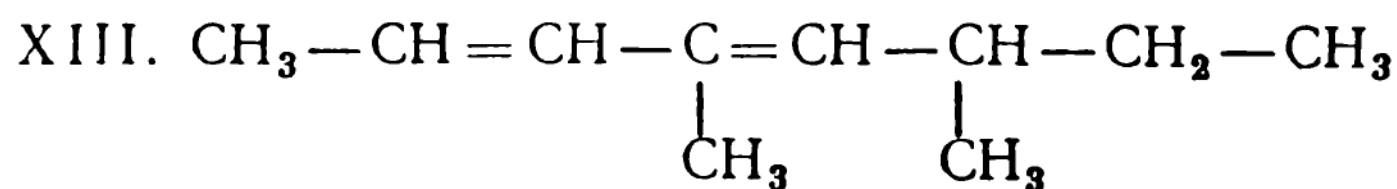
The Liege and IUPAC rules differ from the Geneva rules in the approach to the choice of the main chain and its enumeration: multiple bonds must be included in the main chain (even if the chain is found to be not the longest one) and its numbering must be done so that the multiple bond is indicated by the lowest available number. This is also an expression of the fundamental statement of these nomenclatures, which differentiates them from the Geneva nomenclature: preference is always given to the function (multiple bonds included) rather than to the carbon skeleton (example XIII).



α -Methyl- β -isopropylethylene (R)
2-Methylpent-3-ene (G)
4-Methylpent-2-ene (L, IUPAC)



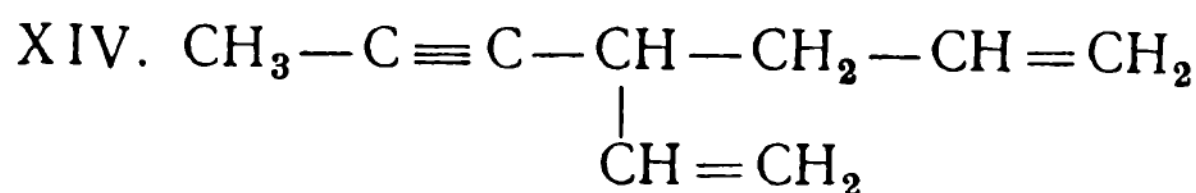
Ethylisobutylacetylene (R)
2-Methylhept-4-yne (G)
6-Methylhept-3-yne (IUPAC)



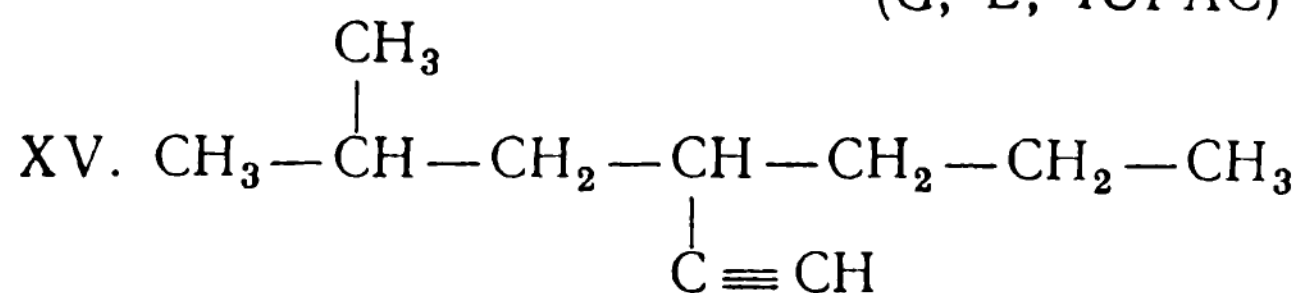
3,5-Dimethylocta-4,6-diene (G)
4,6-Dimethylocta-2,4-diene (IUPAC)

The designations of many unsaturated radicals are used as constituent parts of names of complex unsaturated compounds: some of the names of such radicals are given in Table 3.

These names are used, in particular, for complex highly unsaturated compounds (example XIV) when it is impossible to include all the multiple bonds in the main chain as required by the Liege rules, and also for constructing Geneva names of unsaturated hydrocarbons (example XV):



4-Vinylhept-1-en-5-yne
(G, L, IUPAC)



2-Methyl-4-ethynylheptane (G)
5-Methyl-3-propylhex-1-yne
(L, IUPAC)

TABLE 3

Names of Some Unsaturated Radicals

Formula	Name	Formula	Name
$\text{CH}_2 =$	Methylene	$\text{CH}_3 - \text{CH} =$	Ethylidene
$\text{CH}_2 = \text{CH} -$	Vinyl	$\text{CH}_2 = \text{C} -$	Isopropenyl
$\text{CH} \equiv \text{C} -$	Ethynyl	$\quad \quad $	
$\text{CH}_2 = \text{CH} - \text{CH}_2 -$	Allyl	$\quad \quad \text{CH}_3$	
$\text{CH} \equiv \text{C} - \text{CH}_2 -$	Propargyl	$\text{CH}_3 - \text{C} =$	Isopropylidene
$\text{CH}_3 - \text{CH} = \text{CH} -$	Propenyl	$\quad \quad $	
		$\quad \quad \text{CH}_3$	

NOMENCLATURE OF COMPOUNDS WITH SIMILAR AND DISSIMILAR FUNCTIONS

It may be visualized that organic compounds, in all their variety, arise from hydrocarbons upon replacement of some of their hydrogen atoms by other atoms (halogens, oxygen, nitrogen) or groups (the hydroxyl OH, the amino group NH₂, the nitro group NO₂, the sulpho group SO₃H and many others). Such substituents are called *functions* or *functional groups*; their nature governs primarily the chemical character of an organic compound.

A distinction is made between compounds with similar functions (that is, those containing one type of function, though it may repeat many times in the molecule) and compounds with dissimilar functions (so-called heterofunctional compounds).

Rational Names

In accordance with the general approach characteristic of rational nomenclature, names are composed of the names of radicals added to the name of the prototype, or else to the group name of a given class of organic substances.

The prototype for the names of monoatomic alcohols is the methanol residue C—OH , which is called carbinol (examples XVI-XVIII), for α -glycols—ethylene glycol (example XIX); for carboxylic acids—acetic acid or any other carboxylic acid (examples XX-XXII). The names of aldehydes are formed from the names of the corresponding acids (the word *acid* in the names of the compounds XX-XXII is replaced by *aldehyde*). Group names may be the names of halides (fluoride, chloride, bromide, iodide) (examples XXIII-XXVI), the name ketone for the bivalent residue —CO— (examples XXVII-XXIX), the name amine for the ammonia residue (examples XXX-XXXI). The group name alcohol may be used for the second method of naming alcohols (examples XVI-XVII):

XVI.	$\text{CH}_3\text{—CH}_2\text{—CH—OH}$ CH_3	Methylethylcarbinol; secondary butyl alcohol (<i>sec</i> -butyl alcohol)
XVII.	$(\text{CH}_3)_3\text{C—OH}$	Trimethylcarbinol; tertiary butyl alcohol (<i>tert</i> -butyl alcohol)
XVIII.	$\text{CH}_2=\text{CH—CH}_2\text{—C—OH}$ CH_3 $\text{CH}_3\text{—CH—CH}_3$	Methylisopropylallylcarbinol
XIX.	$\text{CH}_3\text{—CH—CH—C}_2\text{H}_5$ OH OH	α -Methyl- β -ethylethyleneglycol
XX.	$\text{CH}_3\text{—CH—CH}_2\text{—COOH}$ CH_3	Isopropylacetic acid; isovaleric acid; β -methylbutyric acid
XXI.	$\text{CH}_3\text{—CH}_2\text{—CH—COOH}$ CH_3	Methylethylacetic acid; α -methylbutyric acid
XXII.	$\text{CH}_2=\text{CH—CH—COOH}$ CH_3	Methylvinylacetic acid; α -vinylpropionic acid

XXIII.	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{C}-\text{Cl} \\ \\ \text{CH}_3 \end{array}$	<i>tert</i> -Amyl chloride ¹
XXIV.	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}_3 \\ \\ \text{Br} \end{array}$	<i>sec</i> -Butyl bromide
XXV.	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}-\text{CH}_2\text{Br} \end{array}$	Isobutyl bromide
XXVI.	$(\text{CH}_3)_3\text{C}-\text{CH}_2-\text{Cl}$	Neopentyl chloride
XXVII.	$\text{CH}_3-\text{CO}-\text{C}_2\text{H}_5$	Methyl ethyl ketone
XXVIII.	$\text{CH}_3-\text{CO}-\text{C}(\text{CH}_3)_3$	Methyl- <i>tert</i> -butyl ketone; pinacolone
XXIX.	$\text{CH}_3-\text{CO}-\text{CH}=\text{CH}-\text{CH}_3$	Methylpropenyl ketone
XXX.	$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH} \\ \diagup \\ \text{CH}_3 \end{array} - \text{CH}_2 - \text{NH}_2$	Isobutylamine
XXXI.	$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH} \\ \diagup \\ \text{C}_2\text{H}_5 \end{array} - \text{NH} - \text{CH} = \text{CH}_2$	Vinyl- <i>sec</i> -butylamine; N-vinyl- <i>sec</i> -butylamine

Rational names of compounds with several different functions are formed by using, as a prototype, a simpler (usually, monofunctional) compound, for example,

XXXII.	$\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2-\text{CH}-\text{OH} \\ \\ \text{CH}_3 \end{array}$	α -Methyl- β -aminoethyl alcohol; β -hydroxypropylamine
XXXIII.	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}-\text{CH}-\text{COOH} \\ \quad \\ \text{OH} \quad \text{CH}_3 \end{array}$	β -Hydroxy- α -methylbutyric acid
XXXIV.	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-\text{CH}_2-\text{CO}-\text{CH}_3 \\ \\ \text{OH} \end{array}$	Methyl- β -hydroxyisobutyl ketone; diacetone alcohol
XXXV.	$\begin{array}{c} \text{CH}_3-\text{CH}-\text{CH}-\text{COOH} \\ \quad \\ \text{OH} \quad \text{NH}_2 \end{array}$	α -Amino- β -hydroxybutyric acid; threonine

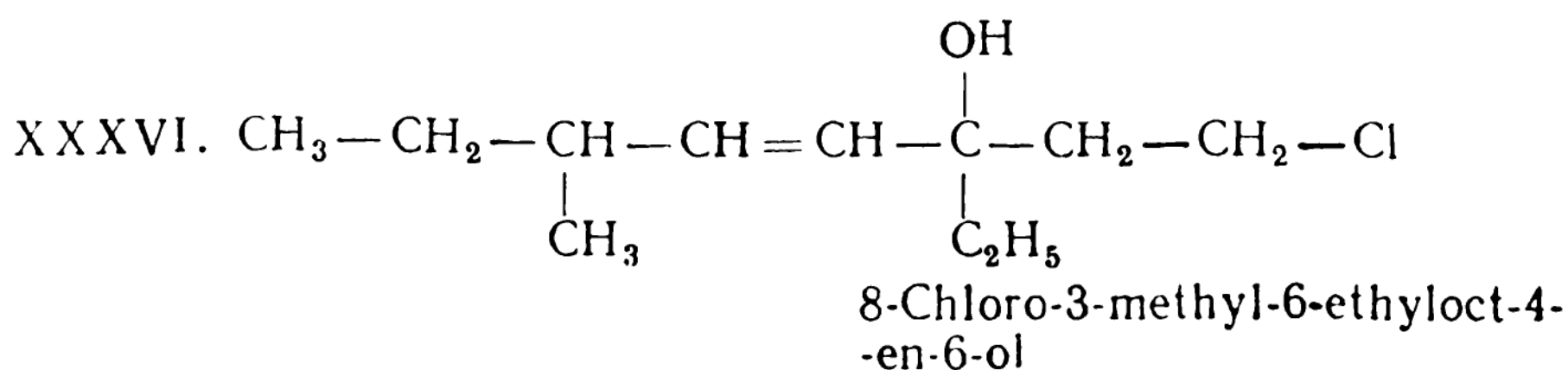
¹ The radical C_5H_{11} was formerly called the amyl (after amyl alcohol $\text{C}_5\text{H}_{11}\text{OH}$); this exception was removed in the IUPAC rules which recommend using the name pentyl for it.

The Geneva names of organic compounds are built in accordance with the generic principle: the stem of the name of each organic compound, whatever the functions it contains, is the name of the corresponding hydrocarbon. The presence of substituents is expressed by adding the following prefixes to the name: *fluoro-*, *chloro-*, *bromo-*, *iodo-*, *nitro-* (NO_2), *nitroso-* (NO), *azido-* (N_3), *amino-* (NH_2), and suffixes for designating the oxygen functions (and their sulphur analogues): *-ol* for the hydroxyl, *-al* for the aldehyde group, *-one* for the keto group, *-oic*, *-ic acid* for the carboxyl group.

The constituent parts of a word-name are placed in a strictly definite sequence, which provides a clear-cut graphical scheme, thereby facilitating the construction and decoding of Geneva names (see Table 4). The sections of the scheme are enumerated in order of falling seniority (the section of the highest seniority is I); within the sections the seniority rises from top to bottom along the vertical, with the exception of section II, where the order of changing seniority is reversed (the most senior radical is methyl).

The carbon atom of the aldehyde, keto, acidic, and other analogous groups is included in the total number of atoms of the carbon skeleton; to remember this, the carbon atom in section IV is separated from the functional group proper by a square bracket.

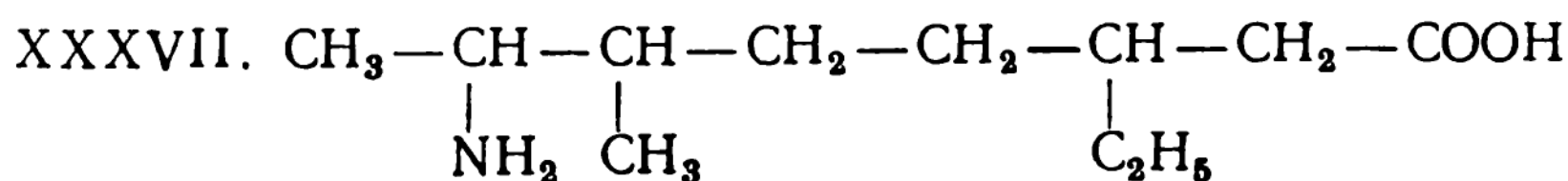
The practical application of the scheme is illustrated by the examples given below. To illustrate Section 17 of the Geneva rules, those compounds are chosen which have an identical carbon skeleton and differ only in the nature and location of multiple bonds and substituents. In coining and decoding Geneva names one has to learn to start with the main chain and then pass to the side chain, and so on, in order of falling seniority of the sections of the scheme.



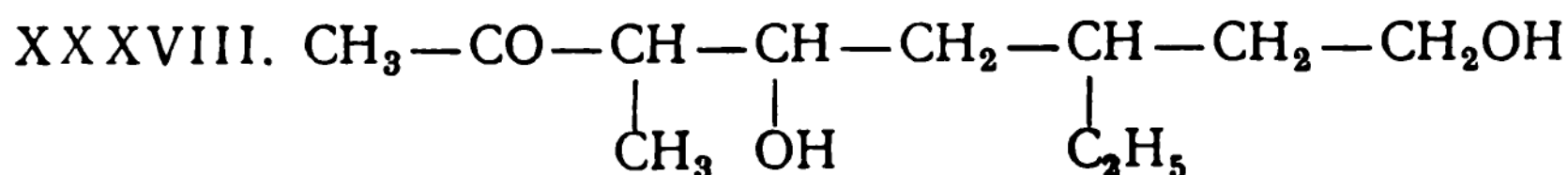
The Scheme of Geneva Names of Acyclic Compounds

TABLE 4

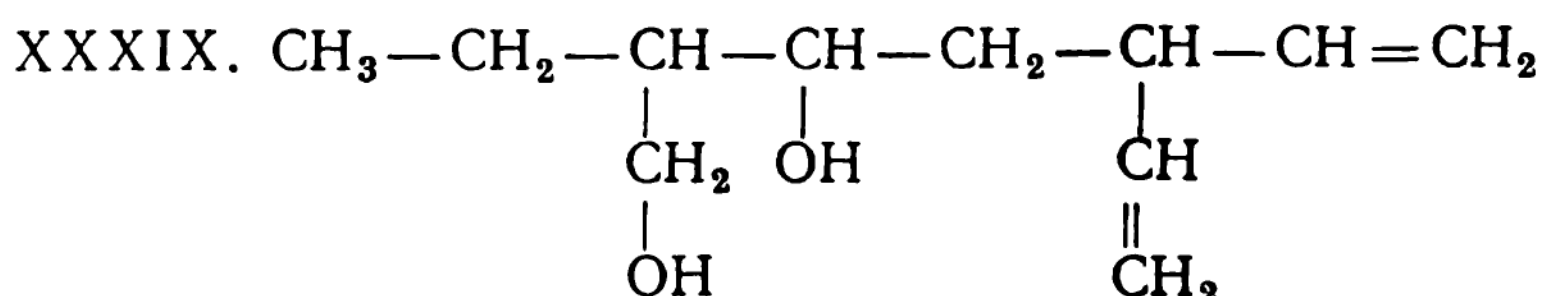
VI Nonfunctional substituents	V Nitrogen functions	II Side chains	I Main chain	III Bonds	IV Oxygen functions and their sulphur analogues
Fluoro—F Chloro—Cl Bromo—Br Iodo—I	—NH ₂ -amino- —NHOH -hydro- xylamino- —NHNH ₂ -hydrazino-	CH ₃ methyl- C ₂ H ₅ ethyl- C ₃ H ₇ propyl- C ₄ H ₉ butyl-	C ₁ meth- C ₂ eth- C ₃ prop- C ₄ but-	C—C -ane C=C -ene C≡C -yne	—OH -ol —SH -thiol —C(=O) -one —C(=S) -thione
Nitroso—NO		C ₅ H ₁₁ amyl-	C ₅ pent-		$\begin{array}{c} \text{O} \\ \parallel \\ \text{—C—H} \end{array}$ -al $\begin{array}{c} \text{S} \\ \parallel \\ \text{—C—H} \end{array}$ -thial $\begin{array}{c} \text{O} \\ \parallel \\ \text{—C—OH} \end{array}$ -oic acid $\begin{array}{c} \text{S} \\ \parallel \\ \text{—C—OH} \end{array}$ -thionic acid $\begin{array}{c} \text{O} \\ \parallel \\ \text{—C—SH} \end{array}$ -thiolic acid $\begin{array}{c} \text{S} \\ \parallel \\ \text{—C—SH} \end{array}$ -dithionic acid —SO ₃ H -sulphonic acid
Nitro—NO ₂		C ₆ H ₁₃ hexyl- and so on	C ₆ hex-		
Azido—N ₃					
Prefixes			Root	Suffixes	



2-Amino-3-methyl-6-ethyloctan-8-oic acid



3-Methyl-6-ethyloctane-4,8-diol-2-one



3-Methylol-6-ethenyloct-7-en-4-ol

The last example shows that in the presence of functions and multiple bonds in side chains, Geneva names lose their direct generic similarity with the name of the original hydrocarbon and also reflect less clearly the functional character of the compound (in example XXXIX one cannot say at once that a diatomic alcohol with two double bonds is meant).

The structures that were given earlier as examples under the heading of rational nomenclature will be given the following Geneva names:

- XVI. Butan-2-ol.
- XVII. 2-Methylpropan-2-ol.
- XVIII. 2,3-Dimethylhex-5-en-3-ol.
- XIX. Pentane-2,3-diol.
- XX. 2-Methylbutan-4-oic acid.
- XXI. 2-Methylbutan-1-oic acid.
- XXII. 2-Methylbut-3-en-1-oic acid.
- XXIII. 2-Chloro-2-methylbutane.
- XXIV. 2-Bromobutane.
- XXV. 1-Bromo-2-methylpropane.
- XXVI. 1-Chloro-2,2-dimethylpropane.
- XXVII. Butan-2-one.
- XXVIII. 2,2-Dimethylbutan-3-one.
- XXIX. Pent-2-en-4-one.
- XXX. 1-Amino-2-methylpropane.

XXXI. 2-Vinylaminobutane.

XXXII. 1-Aminopropan-2-ol.

The names of compounds containing simultaneously several different oxygen functions were not regulated by the Geneva nomenclature; this part of the nomenclature was finished off on the basis of the Geneva principles by the editorial of *Beilstein's Handbuch*. Compounds of this type, given earlier, have the following names in *Beilstein's Handbuch*:

XXXIII. 2-Methylbutan-3-ol-1-ic acid.

XXXIV. 2-Methylpentan-2-ol-4-one.

XXXV. 2-Aminobutan-3-ol-1-ic acid.

IUPAC Names

The modern IUPAC rules, in the part concerned with substitutive nomenclature, develop and detail the Liege rules of 1930, which are not therefore considered here.

In the IUPAC rules, the main chain is chosen so that it contains a function (or the maximum possible number of functions in the case of poly- or heterofunctional compounds), the chain length playing no decisive role. In names of heterofunctional compounds, the designation of only one (principal) function is left in the suffix, the designations of the remaining ones being transferred into the prefix. Functions are designated by means of the prefixes and suffixes given in Table 5. The functions in this table are listed in order of decreasing seniority, i.e., the group that stands higher has preference to be included in the suffix. The square bracket separating, in formulas of certain functions, the carbon from the other part of the function has the same meaning as in the scheme of construction of Geneva names (page 23): the carbon that is separated by a bracket is included in the total number of atoms of the carbon skeleton. It should be firmly kept in mind that the same function may be expressed by a different prefix or suffix, in which the "functional carbon" is omitted from the name of the skeleton and included in the function; examples are *butanoic acid* and *propanecarboxylic acid*, which refer to one compound, the acid C_3H_7COOH . The same difference exists between the suffixes *-nitrile* and *-carbonitrile*, and the prefixes *oxo-* and *formyl-*.

TABLE 5

Designations of Substituents

Class of compounds	Formula	Prefix	Suffix
<i>A. Groups indicated both in prefix and suffix</i>			
Carboxylic acids ¹	—COOH	Carboxy-	carboxylic acid
	$\begin{array}{c} \text{O} \\ \parallel \\ \text{—Cl} \backslash \\ \text{OH} \end{array}$	—	-ic acid
Sulphonic acids	—SO ₃ H	Sulpho-	-sulphonic acid
Nitriles	—CN	Cyano-	-carbonitrile
	—C≡N	—	-nitrile
Aldehydes	—CHO	Formyl-	-carbaldehyde
	$\begin{array}{c} \text{O} \\ \parallel \\ \text{—C} \backslash \\ \text{H} \end{array}$	Oxo-	-al
Ketones	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array}$	Oxo-	-one
Alcohols, phenols	—OH	Hydroxy-	-ol
Thiols	—SH	Mercapto-	-thiol
Amines	—NH ₂	Amino-	-amine

B. Groups indicated in prefixes alone

Halogen derivatives	F, Cl, Br, I	Fluoro-, chloro-, bromo-, iodo-
Nitroso compounds	—NO	Nitroso-
Nitro compounds	—NO ₂	Nitro-
Azides	—N ₃	Azido-
Diazo compounds	—N ₂	Diazo-
Ethers	—OR	Alkoxy-

¹ The functional derivatives of carboxylic acids have their own prefixes *carbethoxy-* for ethyl esters, *carbomethoxy-* for methyl esters, *carbamoyl* for amides.

Table 5 contains only the most widespread prefixes and suffixes; in fact, their number is considerably greater. In particular, there are designations for numerous nitrogen-containing groups, for organometallic functions.

The numbering according to IUPAC rules is carried out so that the principal function (expressed by a suffix) is given the lowest available number.

Some of the previously mentioned structures may be listed as examples:

- XX. 3-Methylbutanoic acid (or 3-methylbutyric acid).
XXVIII. 3,3-Dimethylbutan-2-one.
XXIX. Pent-3-en-2-one.
XXXIII. 3-Hydroxy-2-methylbutanoic acid (or 3-hydroxy-2-methylbutyric acid).
XXXV. 2-Amino-3-hydroxybutanoic acid (or 2-amino-3-hydroxybutyric acid).
XXXVI. 1-Chloro-6-methyl-3-ethyloct-4-en-3-ol.
XXXVII. 7-Amino-6-methyl-3-ethyloctanoic acid.
XXXVIII. 4,8-Dihydroxy-3-methyl-6-ethyloctan-2-one.
XXXIX. 5-Vinyl-2-ethylhept-6-ene-1,3-diol.

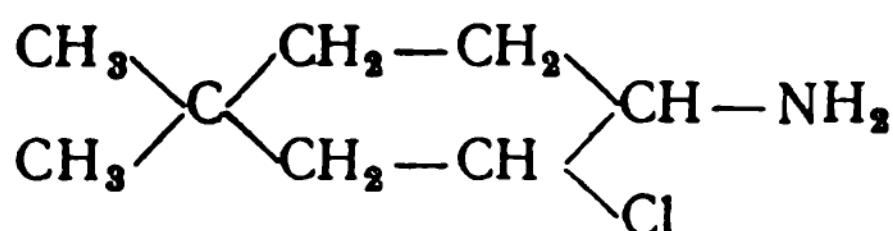
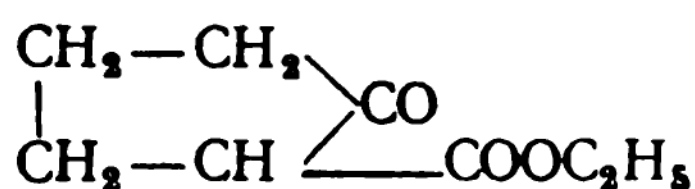
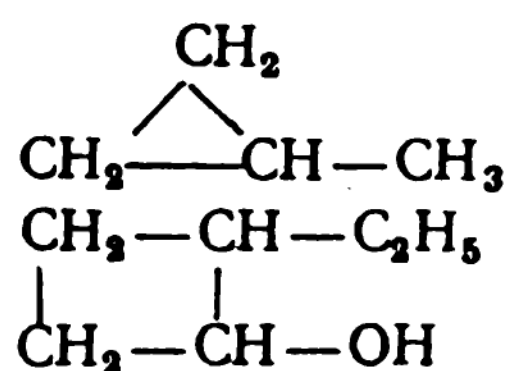
The names of the other structures given above as examples do not differ from the Geneva names. The names of simple structures coincide, as a rule (or differ only in numbering); the IUPAC and Geneva names differ more and more with increasing complexity of the names.

3. CARBOCYCLIC COMPOUNDS

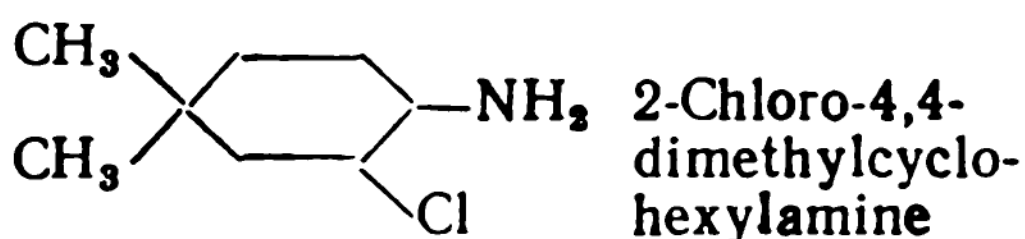
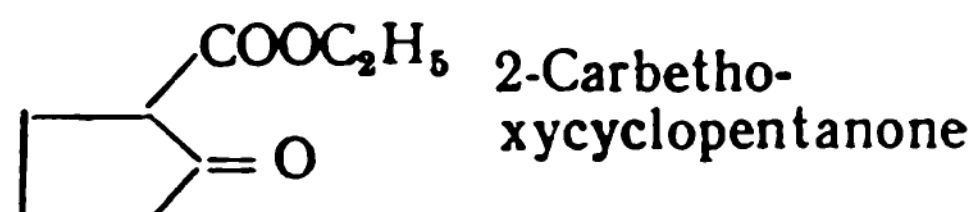
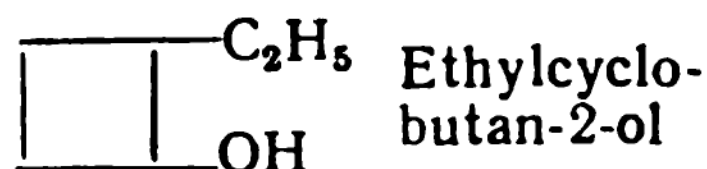
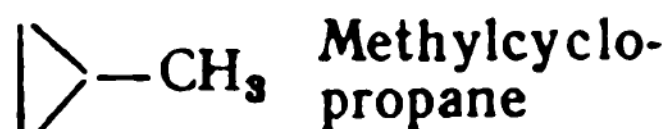
The nomenclature of the simplest cyclic compounds is discussed more briefly since what has been said about the nomenclature of acyclic compounds is largely applicable to carbocyclic compounds: the general principles of building-up of names, the designation of radicals and functions. At the same time, for cyclic and especially heterocyclic compounds there arise not infrequently complexities in composing the name of the cyclic nucleus itself; various methods of forming names of complex cycles are discussed on pages 28, 32-34.

ALICYCLES

Alicyclic compounds are derivatives of the simplest cycles—polymethylenic hydrocarbons (cycloparaffins). Such cycles bear the names of their noncyclic analogues, to which the prefix *cyclo-* is added. To the thus obtained basis of the name there are added prefixes and suffixes which characterize the presence of side chains and functions. The following names may serve as examples:

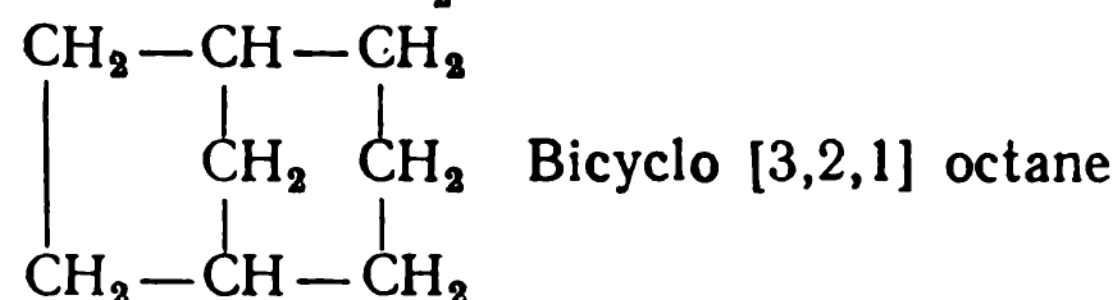


or by convention



The old names *trimethylene* for the cyclopropane ring, *tetramethylene* for the cyclobutane ring, etc., are not specified by the IUPAC rules.

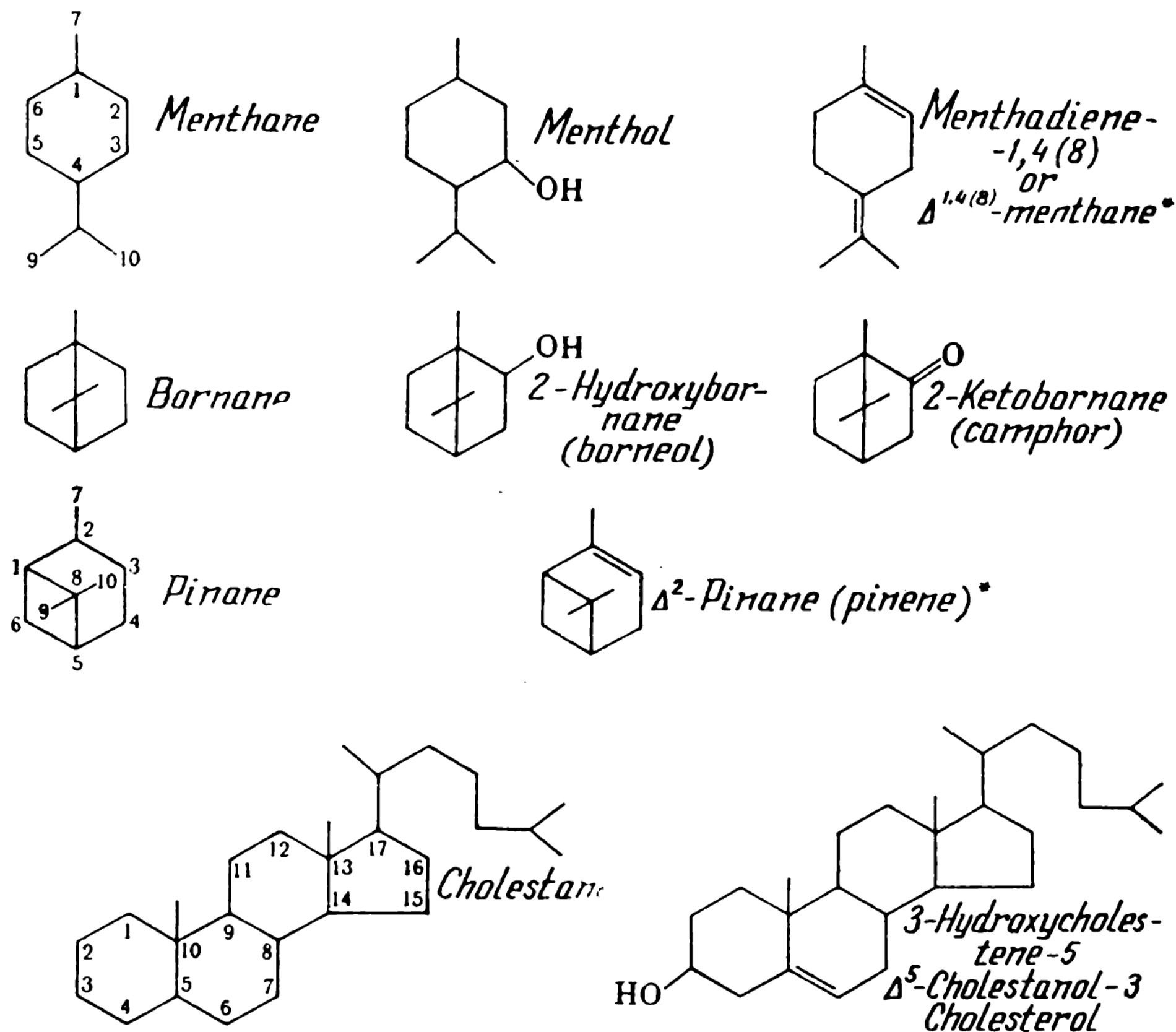
The so-called bridged bicyclic structures, which are primarily represented by compounds of the camphor series, are named according to the Bayer system. In this case a name is formed from the prefix *bicyclo-* and a Greek numeral corresponding to the total number of carbon atoms in the cyclic system. Placed between the constituents of the name is the bracketed code indicating the number of carbon atoms in the bridges linking the key atoms. For example,



The same principle but with a more complex code can be used to coin names of polycyclic nuclei.

For groups of related cyclic compounds there exist regional systems of nomenclature, which are essentially a combination of rational and substitutive names: in these systems, complex cyclic structures are given brief arbitrary names, which are then changed by adding prefixes and suffixes ty-

pical of substitutive nomenclature. Examples are the series of mono- and bicyclic terpenes and steroids:

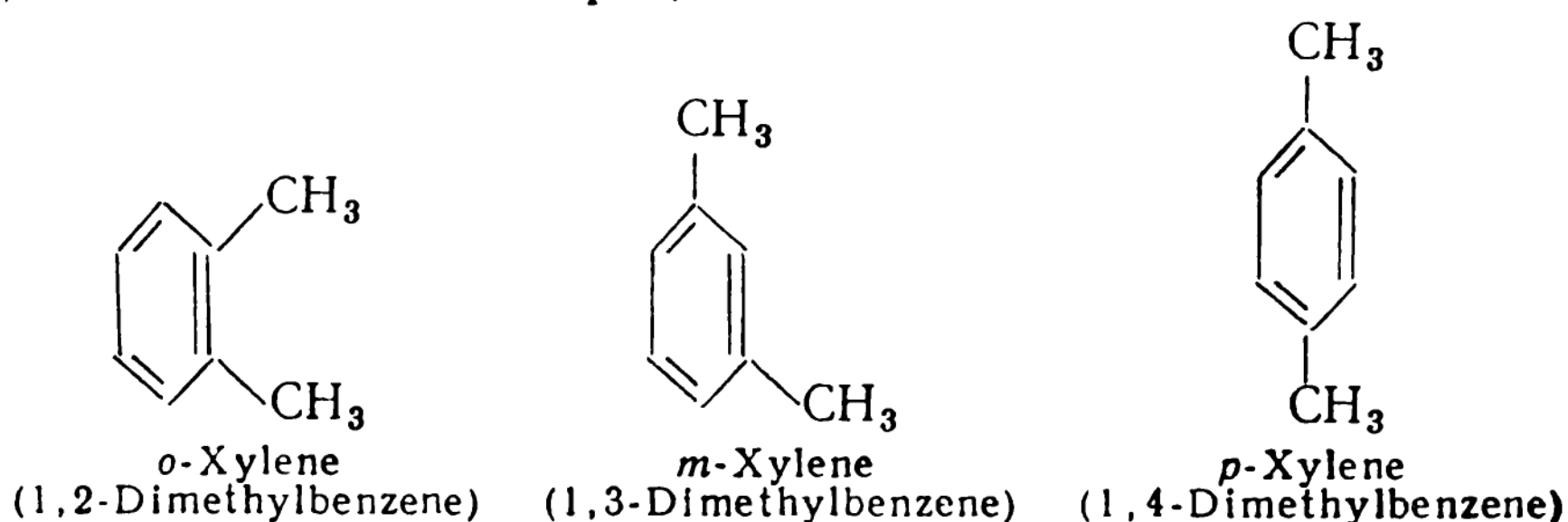


AROMATIC COMPOUNDS

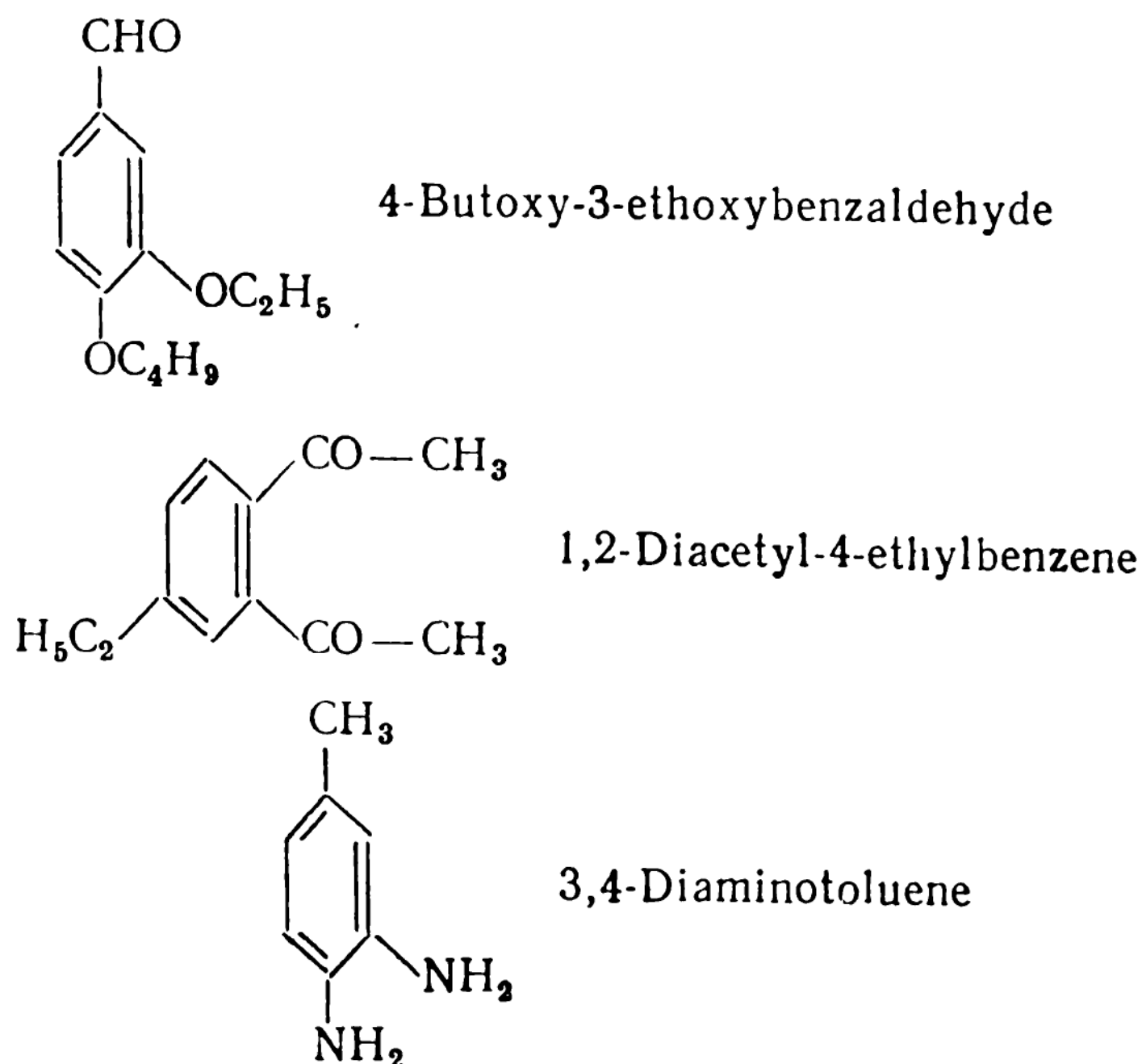
As regards aromatic compounds it was suggested in the Geneva rules to replace the name benzol (the ending of which leads one to assume that there is a hydroxyl function in the compound) by benzene. But this change has become common usage only in English and American nomenclature, while in Russian and German nomenclatures the traditional name benzol is retained.

* In the old literature, the double bonds in steroids and terpenes were designated by the Greek letter Δ with superscripts—the numbers of atoms with double bonds — attached to them. These designations however are not specified by the IUPAC rules.

The isomers of benzene derivatives containing two substituents in the nucleus are named, depending on the relative position of the substituents, as *ortho-* (*o-*), *meta-* (*m-*) or *para-* (*p-*) isomers. For example,

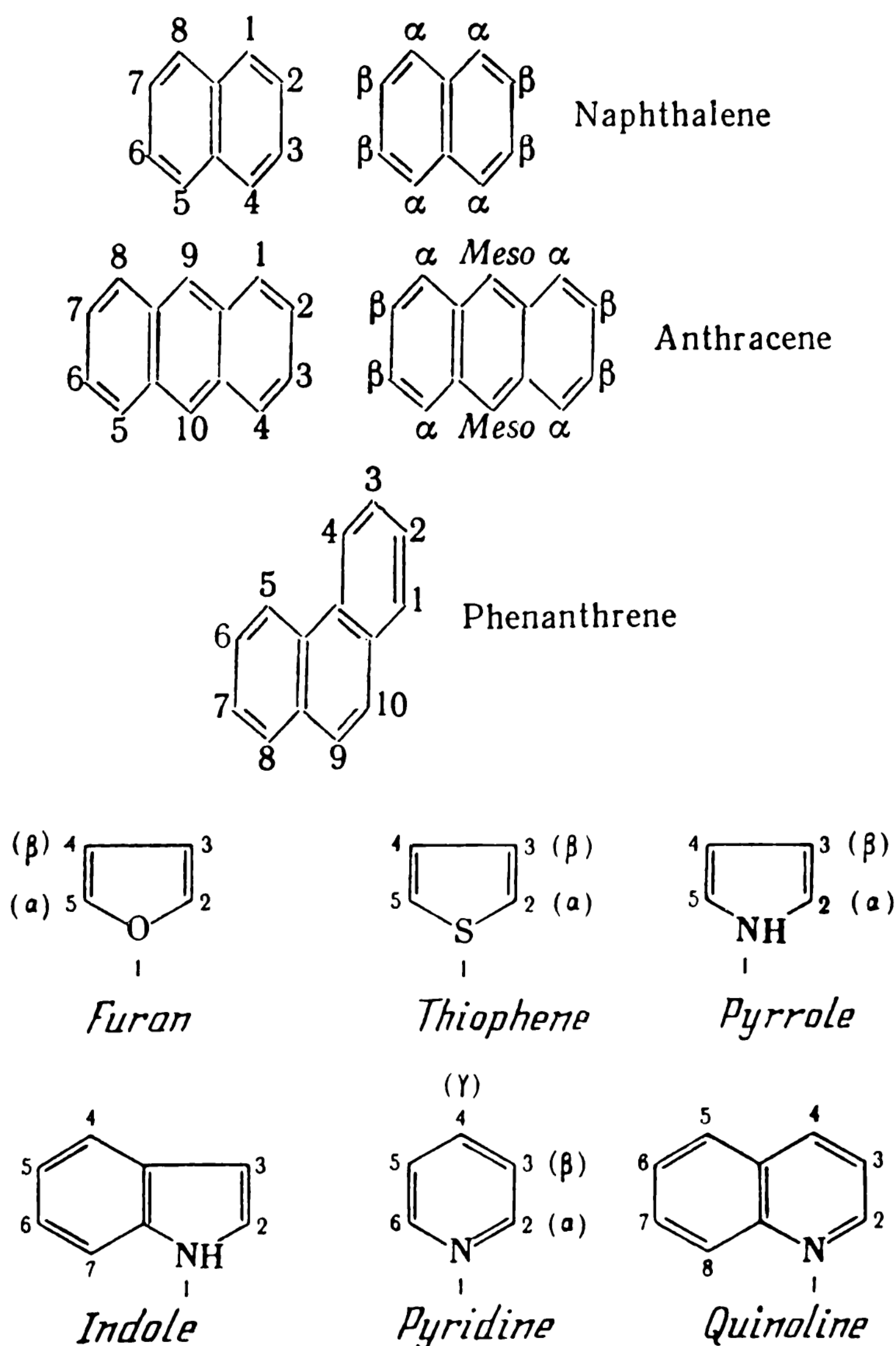


For compounds with three and more substituents in the nucleus these designations become insufficient. In such cases the atoms of the benzene ring are numbered and the positions of substituents are indicated by numerals. According to the IUPAC rules, numbering is primarily determined, as in the case of acyclic compounds, by the position of the higher (denoted in the suffix) function, and its direction is chosen so that the other functions are given the lowest possible numbers. The following names may be cited as examples:



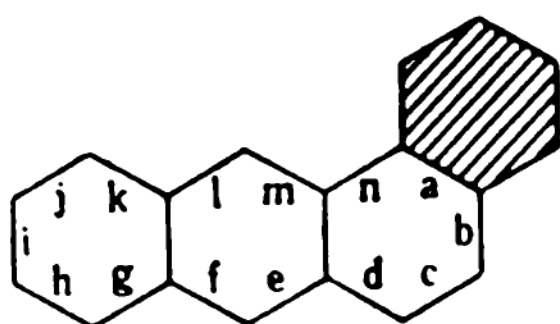
As seen from the last example, not only benzene but also its simplest homologues may be used as the basis of a name.

The same principles are used to build names of the compounds of the naphthalene, anthracene, phenanthrene series, simplest aromatic five- and six-membered heterocycles. It is important to know the numbering adopted for these systems, which, in distinction to benzene, is determined not by the nature and position of substituents but by the nature of the cyclic nucleus itself, i.e., remains always constant for a given ring:

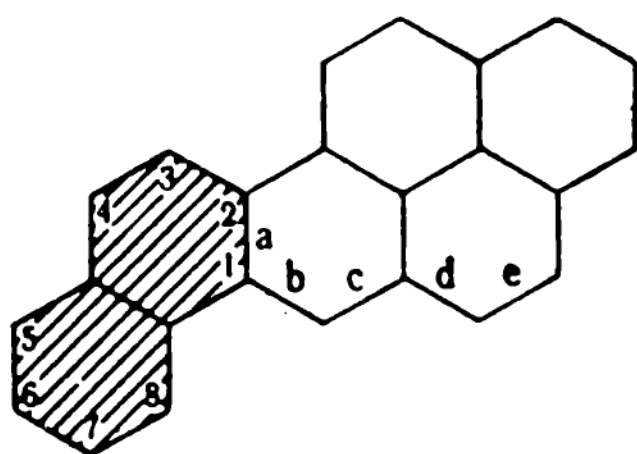


For a large number of more complex carbo- and heterocyclic nuclei the IUPAC rules legislate for recommended trivial names and the adopted numbering of atoms. The names of more complex polycyclic nuclei are recommended to build according to the Patterson system.

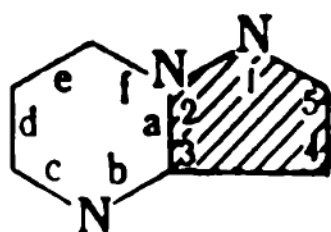
By the Patterson system, a complex condensed system (carbo- or heterocyclic) is split into two constituent parts and its name is built up as a combination of the names of these constituents. To designate the type of fusion of the constituents the peripheral bonds of one of them (the parent structure) are denoted by roman letters and the code placed in square brackets indicates the bond to which the second part is fused (the fused structure). If the fused structure is asymmetrical, an indication is also made as to which of its atoms are engaged in ring fusion. Examples are the following schemes in which the fused structure is shown hatched:



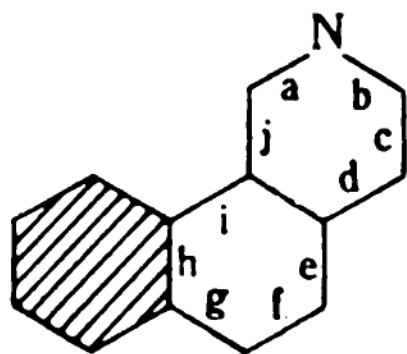
Benz [a] anthracene



Naphtho [2,1-a] pyrene



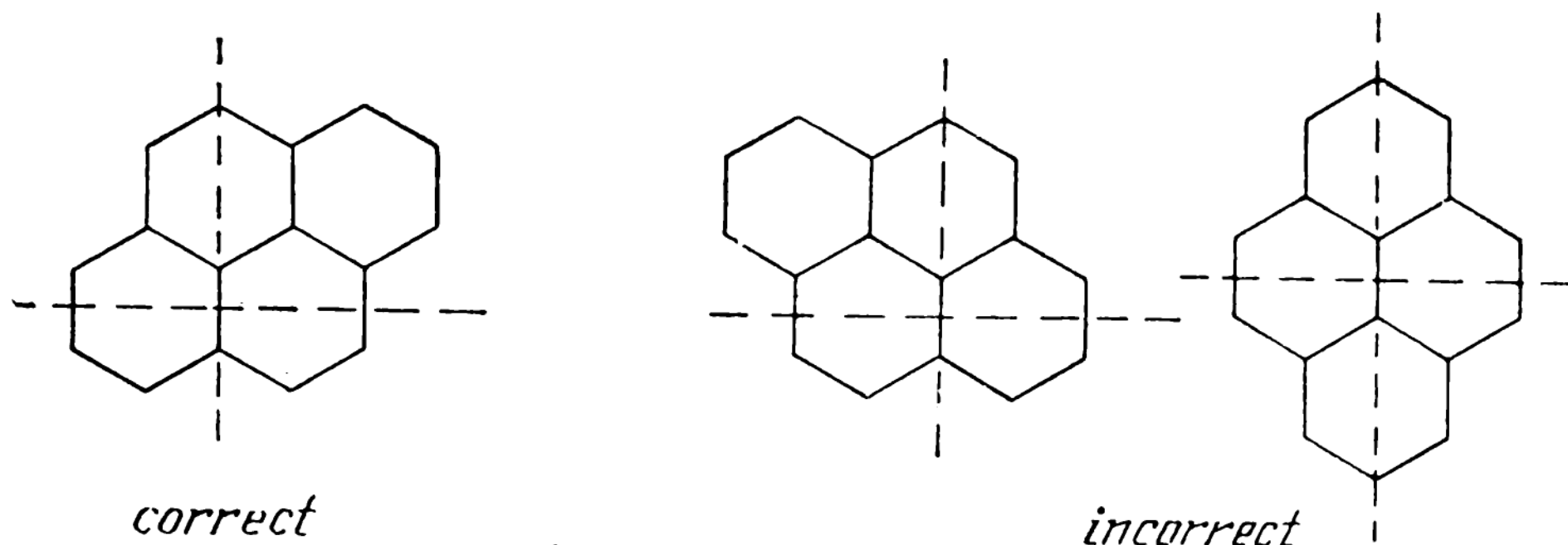
Pyrazolo [3,2-a] pyrimidine



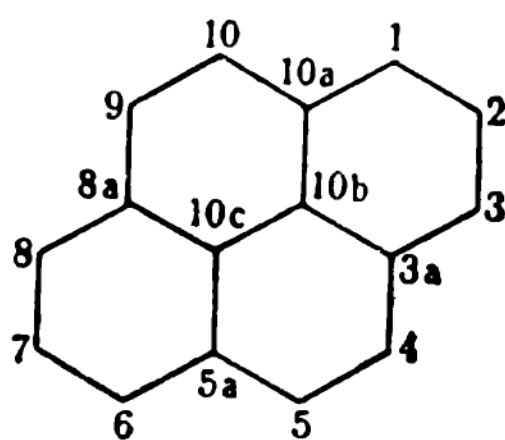
Benzo [h] isoquinoline

The structure as a whole has its own numbering different from the numbering of its constituent parts. To determine the order of numbering the formula is oriented in the plane so that the largest number of rings form a horizontal row,

as much as possible of the remainder of the formula being arranged in the top right quadrant (the middle of the first row being the centre of the circle). For example:



In the formula oriented in this way the numbering proceeds clockwise round the periphery, starting in the right-hand ring of the top row at the first atom not engaged in ring fusion. The atoms engaged in ring fusion (i.e., at the “valley” positions) are not numbered: if necessary, they receive roman letters after the numerals of the preceding atom. The structure of pyrene oriented as indicated above will be numbered as follows:

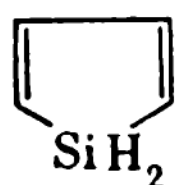


4. HETEROCYCLES

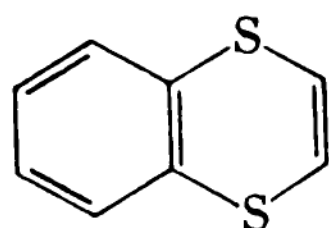
For naming complex heterocyclic structures that have no adopted trivial names the IUPAC rules recommend using the Patterson system described above, that is, the names of simple hetero- and carbocycles are used, or the so-called “a-system”, which is briefly discussed below.

According to the a-system, the names of heterocyclic compounds are formed from the names of the corresponding carbocyclic systems with addition of a prefix, characterizing the type of heteroatom, and of a locant, a numeral denoting the position of the heteroatom.

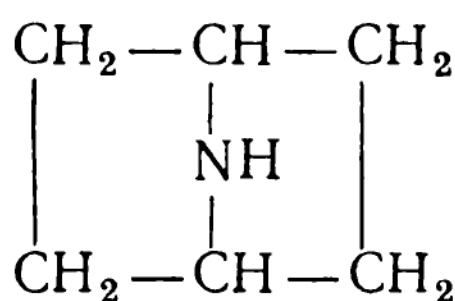
Thus, the nitrogen atom is denoted by *aza*, the oxygen atom by *oxa*, the sulphur atom by *thia*, etc. For example, according to the a-system pyridine is azabenzene and quinoline is 1-azanaphthalene. Of course, it is pointless to use the a-system for such simple compounds with well-established trivial names. In more complex cases the use of the a-system enables one to build up relatively simple and clear-cut names, for example,



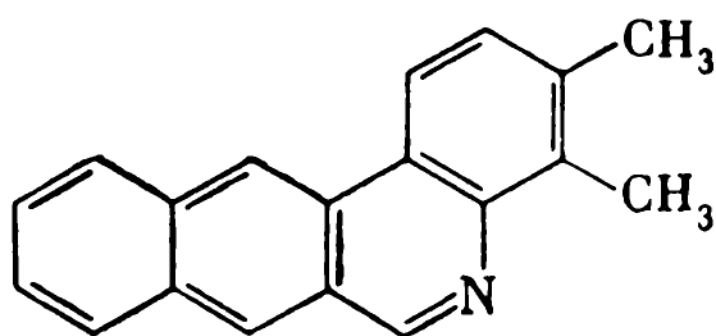
Silacyclopenta-2,4-diene



1,4-Dithianaphthalene



7-Azabicyclo [2,2,1] heptane



3,4-Dimethyl-5-azabenz[a]anthracene

5. SOME PROBLEMS OF THE PRACTICAL APPLICATION OF ORGANIC NOMENCLATURE

Knowledge of organic nomenclature is most often needed by the chemist for the purpose of constructing structural formulas from names encountered in the literature. At the same time the chemist rather often has to solve the reverse problem—to form a name from the formula. The latter task is more involved and requires a thorough knowledge of the rules of organic nomenclature.

The need to compose names from formulas most often arises when one has to collect literature data on a compound. In such a case, a knowledge of the names of a particular compound according to this or that nomenclature is insufficient; one has to know what nomenclature is used in a given literature source.

The starting points to be used by the organic chemist for literary search are *Beilstein's Handbuch* ("Handbuch der organischen Chemie") and the indexes of abstract journals such as *Chemical Abstracts* (published by the American Chemical Society), *Chemisches Zentralblatt* (the German counterpart of Chemical Abstracts) and *RZh Khimiya* (Referativnyi Zhurnal Khimiya, USSR).

The least knowledge of organic nomenclature is required in using *Beilstein's Handbuch*. But in this case one has to know the principle on which this handbook is based. As known, organic compounds in it are arranged in order of increasing complexity of their structural formulas—in general outline according to principal sections of organic chemistry (acyclic, carbocyclic, heterocyclic compounds), by the homologous series and the functions involved. A detailed consideration of the system of arrangement of organic compounds in *Beilstein's* is outside the scope of the present book. It is important to remember that *Beilstein's Handbuch* lists all current names for each substance. Thus, having found a compound by its structural formula, one can get information concerning the names under which it can be sought for in other sources. Especially valuable from this point of view are the names given in the third supplementary series covering the 1929-1949 period since it contains not only rational and Geneva names but also more up-to-date Liege names.

The second most important key to the literature is the indexes of abstract journals, both subject and formula indexes. The use of such indexes requires a knowledge of nomenclature and of the system of organization of the indexes themselves.

The subject index of *Chemical Abstracts* alone covers all chemical substances that have been mentioned in the abstracts. The subject indexes of other abstract journals—*Chemisches Zentralblatt* and *RZh Khimiya*—include only relatively simple organic compounds with well-known trivial names; all others have therefore to be looked for with the aid of a formula index.

As in any subject index, the names of organic compounds in *Chemical Abstracts* are arranged in alphabetical order. An attempt to find, say, nitrobenzene under the letter "n" in this index, would fail because of "inversion" of the names

included in the subject index of *Chemical Abstracts*. By inversion is meant artificial alteration of the order of the constituent parts of a word-name so that its most important part—the main chain or the cyclic nucleus with the principal function—is placed first. This order enables creating “nests” of structurally related compounds in the alphabetical index. For example, the entry under “benzene” occupies up to 10 pages. It covers, in alphabetical order, numerous halogeno-, alkoxy-, and nitro derivatives of benzene. For example,

Benzene

— — — — 1-allyl-2,3,4,5-tetramethoxy-
— — — — 2-bromo-1-methylethyl-
— — — — 1,2,4-trimethoxy-5-(2-nitro-2-butenyl)-

The entry under “2-decanol” contains, among others, the following compounds:

2-Decanol

— — — — 1-amino-1,2-diphenyl-
— — — — 2-methyl-

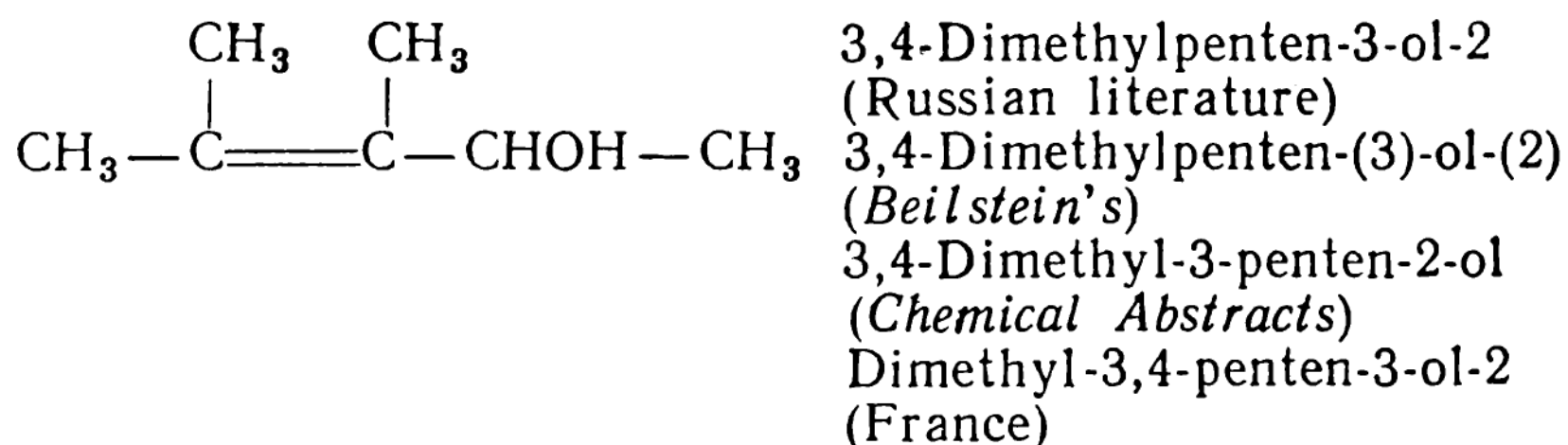
As seen from these examples, in *Chemical Abstracts* the first place on inversion is given to the principal function with that part of the carbon skeleton to which it is attached. For instance, the entry “benzaldehyde” includes various alkyl, halogen, nitro-, and alkoxy derivatives of benzaldehyde; if the nucleus contains, in addition, a carboxyl group, then the corresponding compound must be looked for as the formyl derivative of benzoic (or any other) acid. The entry “2-hexanone” contains its derivatives with any hydrocarbon radicals (aliphatic, aromatic, heterocyclic) provided that they contain no functions higher than the ketonic function (see Table 5).

The USSR abstract journal *RZh Khimiya* is based on a different principle. The subject index of this journal does not practically contain names of chemical substances (with the exception of about a hundred trivial names of amino acids, vitamins, and some steroids). In order to find information on organic compounds in *RZh Khimiya* one has to make use of the formula index (organized according to the Hill system). The names given under one empirical formula may naturally refer to different substances: these names are cited in the same form as they appear in the abstract, i.e., use is made of the

names given by the author of the research paper. Thus, nomenclature may be varied. Entries (within a single general formula) are formed by inversion of names.

The formula index of *Chemisches Zentralblatt* is arranged in a similar way. The difference is that no inversion of names is used here. Besides, the subject index contains names of a considerably larger number of chemical substances than the subject index of *RZh Khimiya*.

Certain difficulties arise because of the lack of uniformity in the methods of writing names of compounds—the customs of publishing journals vary from one country to another as regards the placement of numerals, the use of hyphens and parentheses, italicizing, punctuation, etc. For example:



The ambiguity of names of compounds, the various conventions in writing them, all this, of course, creates additional difficulties in the mastery of the material of organic chemistry. These difficulties, however, are often found to be not too serious as they seem at first glance. The general principles of structural nomenclatures are identical. They may be formulated as follows:

1. The name of an organic compound describes its structural formula.

2. The basis of a name is formed by the main chain (nucleus), the choice of which is regulated by definite rules (which are different in different systems of nomenclature).

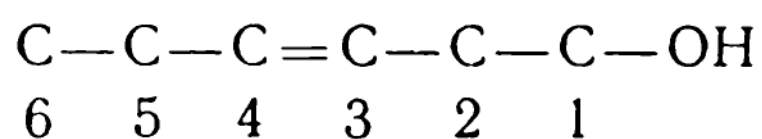
3. The atoms of the main chain (nucleus) are numbered in a definite order (this order of numbering depends on a concrete system of nomenclature).

4. The positions of side chains and other substituents are designated by prefixes and suffixes with indication of a numeral (locant) for the atom of the main chain (nucleus) at which the substituent stands.

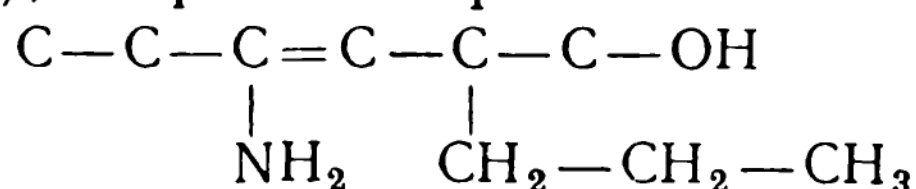
Rational names can usually be recognized by the mode of their construction and by the use of Greek letters (not nu-

merals) as locants. The names built according to the Geneva, Liege and IUPAC rules are outwardly similar, and not infrequently, only when the name of a compound has been decoded, one can understand according to what system of nomenclature it is formed. For identification it is not important whether it is a Geneva or Liege name since the approach to deciphering may be the same.

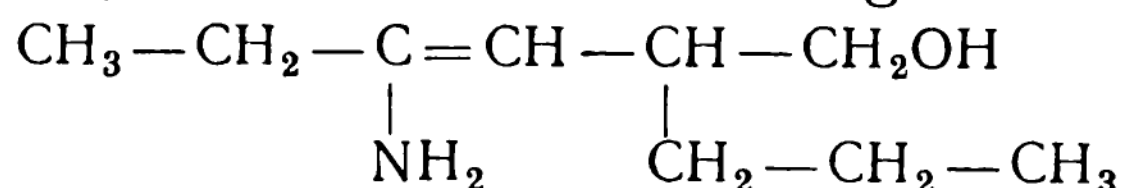
Let us suppose that we are to build a structural formula by the name 4-amino-2-propylhex-3-en-1-ol. First we must single out the main skeleton with the principal function, which in this case is "hex-3-en-1-ol", i.e., a fragment having the following formula



Having enumerated the carbon atoms in the main skeleton (the main chain), we place the prefixes contained in the name:



and supplement the structure with the required number of hydrogen atoms, as a result of which we get the final formula:



Now we see that the name was composed according to the Liege rules: the principal chain chosen is not the longest one and includes all the functions present. The same procedure can be used in deciphering other names.

In coining names of complex organic compounds use is made, as constituents, of the designations of not only the simplest radicals listed in Tables 1 and 3, but also of other more complicated ones. A list of radicals which is part of the rules contains several hundreds of names. The most widely used radicals are presented in Table 6.

6. MATERIAL FOR EXERCISES

The material for exercises consists of three parts. The first part covers general questions concerning primarily the use of the literature—*Beilstein's Handbuch* and indexes of abstract journals.

TABLE 6

Names of Some Radicals According to IUPAC Rules

Name	Formula	Name	Formula
Acetonyl	$\text{CH}_3\text{—CO—CH}_2\text{—}$	α -Furyl	
Acetoxy	$\text{CH}_3\text{—COO—}$	Hydrazino	$\text{H}_2\text{N—NH—}$
Acetyl ¹	$\text{CH}_3\text{—CO—}$	Hydroxylamino	HO—NH—
Acetylamino ²	$\text{CH}_3\text{CO—NH—}$	Imino	—NH—
Allyl	$\text{CH}_2=\text{CH—CH}_2\text{—}$	Isobutyl ³	$(\text{CH}_3)_2\text{CH—CH}_2\text{—}$
Anilino	$\text{C}_6\text{H}_5\text{NH—}$	Isopropenyl	$\text{CH}_2=\text{C}(\text{CH}_3)\text{—}$
Benzenesulphonyl	$\text{C}_6\text{H}_5\text{SO}_2\text{—}$		
Benzoyl	$\text{C}_6\text{H}_5\text{CO—}$	Mesityl	
Benzyl	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$		
Benzylidene	$\text{C}_6\text{H}_5\text{—CH=}$		
1-Butenyl	$\text{CH}_3\text{—CH}_2\text{—CH=CH—}$	Methoxy	$\text{CH}_3\text{O—}$
	$=\text{CH—}$	Methyl	$\text{CH}_3\text{—}$
2-Butenyl	$\text{CH}_3\text{—CH=CH—CH}_2\text{—}$	Methylallyl (metallyl)	$\text{CH}_2=\text{C}(\text{CH}_3)\text{—CH}_2\text{—}$
Butoxy	$\text{CH}_3\text{—(CH}_2)_3\text{O—}$		
Butyl	$\text{CH}_3\text{—(CH}_2)_3\text{—}$	Methylene	$\text{—CH}_2\text{—}$
Cyclohexyl		Methylenedioxy	$\text{—O—CH}_2\text{—O—}$
		Methylidyne (methine)	$\text{HC}\equiv$
Cyclopentadienyl		Naphthyl	$\text{C}_{10}\text{H}_7\text{—}$
		Phenoxy	$\text{C}_6\text{H}_5\text{O—}$
		Phenyl	$\text{C}_6\text{H}_5\text{—}$
Cyclopropyl		Phenylacetyl	$\text{C}_6\text{H}_5\text{CH}_2\text{CO—}$
Dimethylamino	$(\text{CH}_3)_2\text{N—}$	Propyl	$\text{C}_3\text{H}_7\text{—}$
Epoxy	—O—	Styryl	$\text{C}_6\text{H}_5\text{—CH=CH—}$
Ethyl	$\text{C}_2\text{H}_5\text{—}$	α -Thenyl	
Ethylamino	$\text{C}_2\text{H}_5\text{NH—}$	Thienyl	
Ethylidene	$\text{CH}_3\text{—CH=}$		
Ethynyl	$\text{HC}\equiv\text{C—}$	Tolyl	$\text{CH}_3\text{—C}_6\text{H}_4\text{—}$
		Trityl	$(\text{C}_6\text{H}_5)_3\text{C—}$
Furfuryl		Vinyl	$\text{CH}_2=\text{CH—}$
		Vinylidene	$\text{CH}_2=\text{C=}$

¹ Analogously, $\text{C}_3\text{H}_7\text{CO}$ is *propionyl*, $\text{C}_4\text{H}_9\text{CO}$ is *butyryl*, $(\text{CH}_3)_2\text{CHCO}$ is *isobutyryl*, $\text{C}_5\text{H}_{11}\text{CO}$ is *valeryl*, etc.

² Analogously, *formylamino*, *propionylamino*, *benzoylamino*, etc.

³ The prefix *iso-* is also used for all other alkyls having the structure $(\text{CH}_3)_2\text{CH—(CH}_2)_n\text{—}$.

The second part lists the names of various organic compounds built according to different systems of nomenclature and written in various ways (in the form they are found in literature sources). These names can be used for exercises in the building of structural formulas, and in carrying out the inversion.

The third part contains structural formulas from which one can compose names of various types—rational (where it is possible), Geneva, and those built according to the IUPAC rules. It is recommended to pay great attention to modern IUPAC nomenclature since other types of names are more seldom used.

At the end a key is given, in which the correspondence between the names in the second part and the formulas in the third part is established, i.e., answers to possible assignments are given in tabular form.

GENERAL QUESTIONS

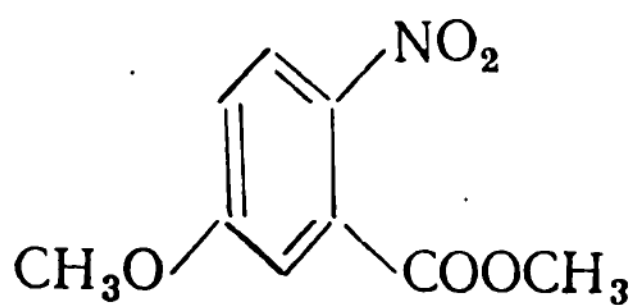
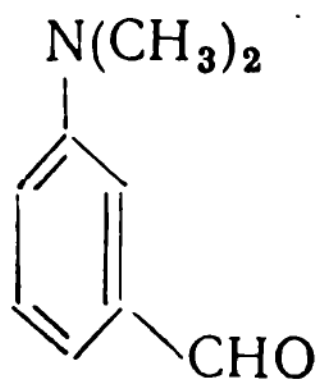
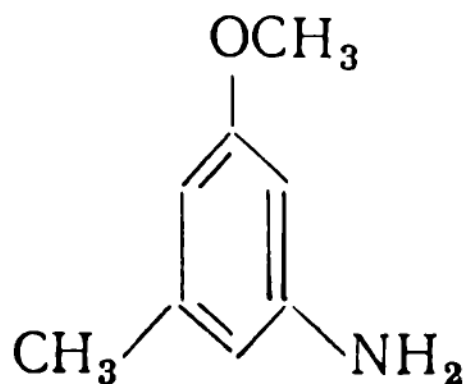
1. What sources must be used in order to collect, in the most efficient way, all literature data on a particular organic compound?

2. What information must a correctly formulated literature reference contain: a reference to a journal article and a reference to a book?

3. What annual and cumulative indexes are published as supplements to *Chemical Abstracts*, *Chemisches Zentralblatt*, and *RZh Khimiya*?

4. What problems can be solved in working with the literature with the aid of an author index?

5. What does the "inversion" of names mean? How will the names of the following compounds look in "inverted" form?



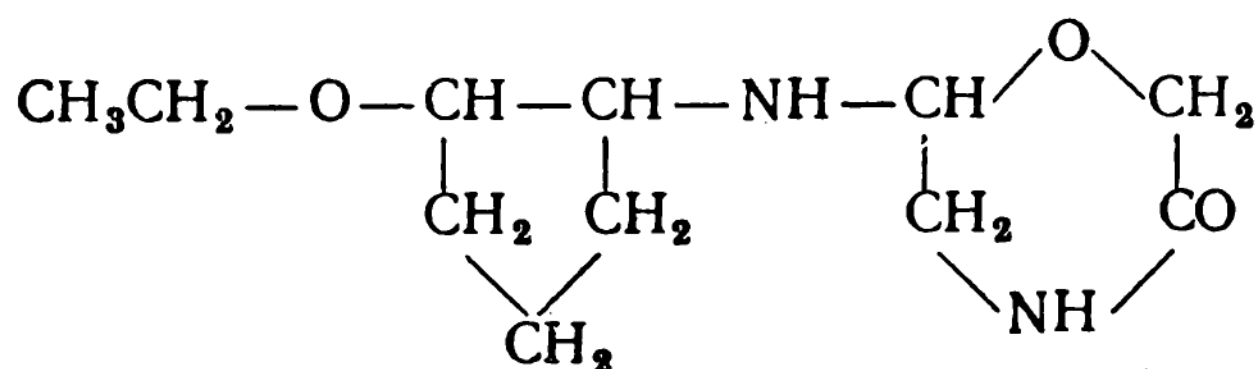
6. What indexes are there available in *Beilstein's Handbuch*? What is the system of their organization?

7. How can you establish the year of publication of a research article in a journal with the aid of *Beilstein's Handbuch* (references indicate, as a rule, only the number of a volume of a journal)?

8. What substituents are referred to as non-functional in Beilstein's system?

9. In what order are the derivatives of methane containing from one to four non-functional substituents arranged in *Beilstein's Handbuch*?

10. In which section of *Beilstein's Handbuch* should one look for succinic anhydride, the lactam of γ -aminobutyric acid, dioxane and the compound given below?



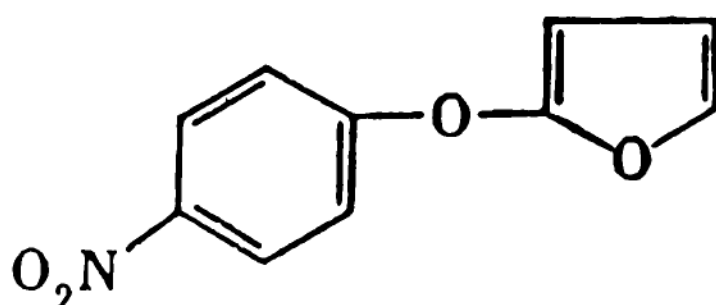
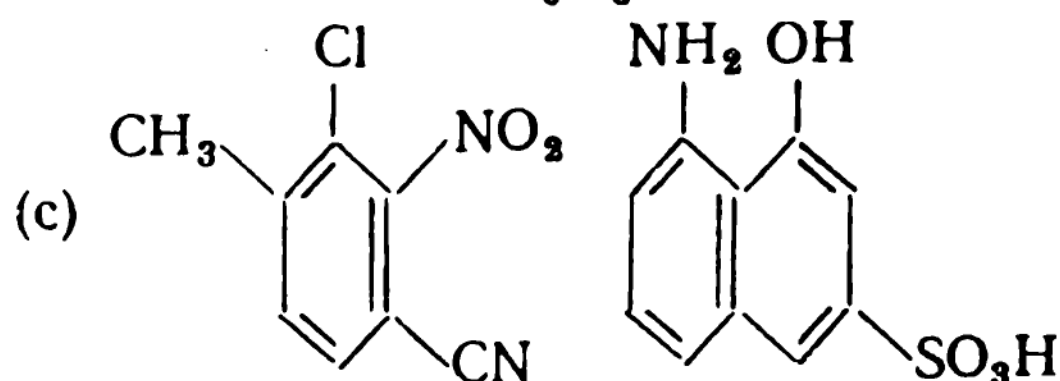
11. How are mercaptans and their derivatives and also other sulphur-containing compounds arranged in *Beilstein's Handbuch*?

12. Among the derivatives of which entries must one look for the following compounds in *Beilstein's Handbuch*?

(a) $\text{Cl}-\text{CH}_2-\text{OCH}_3$

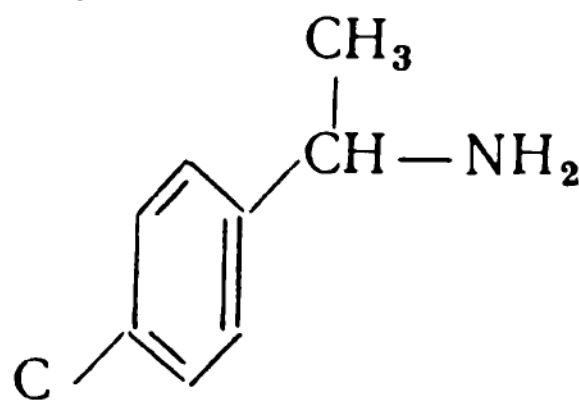
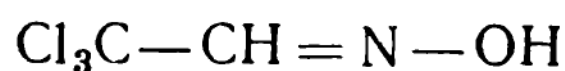
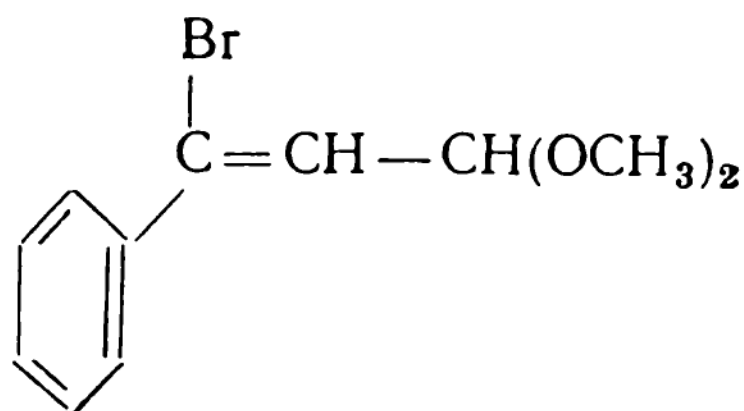
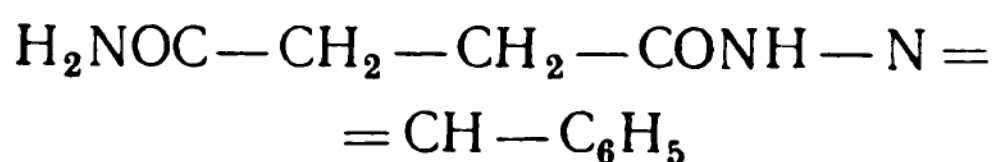
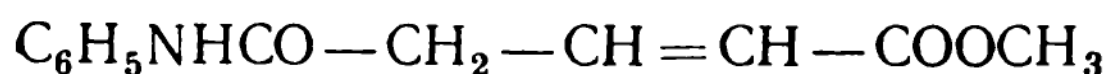
$$\text{Cl}_2\text{CH}-\text{OCH}_3, \text{CH}_3-\text{CHOH}-\text{N}(\text{CH}_3)_2, \text{ClCH}_2-\text{CON}(\text{CH}_3)_2$$

(b) $\text{C}_6\text{H}_5\text{NH}-\text{CO}-\text{CH}_2\text{Cl}$, $\text{C}_6\text{H}_5-\text{C} \begin{array}{l} \nearrow \text{NH}-\text{COCH}_3 \\ \text{---} \text{NHOH} \\ \searrow \text{OCH}_3 \end{array}$

$$\text{CH}_3-\text{C}_6\text{H}_4-\text{CO}-\text{NH}-\text{COCH}_3, \quad \text{C}_6\text{H}_5-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}_2\text{CH}_2\text{NH}_2, \\ \text{C}_6\text{H}_5-\text{CONH}-\text{CH}_2\text{CH}_2\text{OH}$$


13. Among the derivatives of which entry must one look for the following compounds in *Beilstein's Handbuch*: ethyl α -hydroxy- β -dimethylaminoisobutyrate, ethyl α -acetaminoisobutyrate, methyl α -benzoylamino-propionate, a Schiff base from benzaldehyde and 1-amino-3-cyanopropane?

14. Under what empirical formula and under what name should one locate the following compounds in the formula index of *Beilstein's Handbuch* and in the formula index of *Chemical Abstracts*?



NAMES¹

1. 4-Propyl-5-isopropyloctane.
2. 2,3,5-Trimethylhexane.
3. Di-*tert*-butylmethane.
4. Methylvinylallylmethane.
5. 4,4-Dimethylpentene-1.
6. 4-Methylhexene-2.
7. 2-Methyl-6-methyleneoctadiene-1,7.
8. 4-Ethenyl-5-ethynyloctene-4.
9. 2-Chloro-3-methylbutane.
10. 1-Chloro-2,2-dimethylpropane.
11. 4-Methylhexanol-3.
12. 2-Ethylhexanediol-(1,3).
13. 2-Ethylbuten-2-ol-1.
14. Δ^1 -Octenol-(3).
15. 2,2,4-Trimethyl-3-penten-1-ol.

¹ The names are given in the form they were written in the original literature.

16. 1,4-Dimethyl-1,4-di-*tert*-butyl-butyne-(2)-diol-(1,4).
17. 4-Methylpentanal-1.
18. Methylethylallylacetic aldehyde.
19. Penten-3-one-2; 3-methyl.
20. 3,7-Dimethyl-2,6-octadienal.
21. 4-Methylpentanone-2.
22. 5-Methylhexen-3-one-2.
23. Allyldiacetylmethane.
24. 1-Methylpentanediamine-1,5.
25. 2-Methylhexanoic-6-acid.
26. Heptane-4-carboxylic acid.
27. Methylpropylacetic acid.
28. α -Vinylisovaleric acid.
29. 3-Methyl-3-hexene-1,1,6,6-tetracarboxylic acid.
30. Hexen-4-yn-2-oic acid.
31. Heptene-3-carboxylic acid-3.
32. Penten-2-ol-1; 3-methyl-5-methoxy.
33. 9-Ethoxy-2,6,8-trimethylnonadien-(2,7)-ol-(6).
34. 7-Oxy-3,7-dimethyloctanal.
35. 5-(Diethylamino)-4-methyl-2-ethyl-2-pentenal.
36. Pentamethyl-2,2,5,6,6-hexanol-5-one-3.
37. 3,5-Epoxy-4,4-dimethylhexanone-2.
38. 3-Chloro-6-oxy-5-methylhexen-3-one-2.
39. 1-Oxypentanecarboxylic-3 acid.
40. β,β -Di(chloromethyl)-lactic acid.
41. 3-Oxy-2,2-dimethylbutanoic-4 acid.
42. 2,4-Dioxohexanoic acid.
43. Butene-2; 1,4-dicyano-2-chlorine.
44. Methyl-3-aminopropyl ester.
45. 1,1,1-Trichloro-3-aminopentanol-2.
46. 2-Acetamido-3-oxohexanedioic-1,6 acid.
47. 8-Amino-4-acetyloctanoic acid.
48. Propyl-isopropyl-4-cyclohexene.
49. Hydroxy-3-triphenyl-3,4,5 cyclohexanone.
50. 2-Chloro-6,6-dimethylcyclohexanone.
51. β -(2-Ketocyclohexyl)-propionic acid.
52. 3-Ethoxy-1(1-nitrocyclohexyl)-hexen-4-one-1.
53. 3-Chloro-2-oxy-6-cyclohexylhexen-3-oic acid.
54. 6-(3-Chloro-2-oxycyclohexyl)-hexen-3-oic acid.
55. 4,5-Dichloro-2[4-chloro-2(oxy-methyl)-5-oxohexen-3-yl] cyclohexanecarboxylic-1 acid.

56. 2-(Diethoxymethyl)-1,3,3-trimethylnorbornane.
57. 1,3-Dichloro-2-bromo-4,6-dinitrobenzene.
58. 1,2,4-Trimethoxy-5-(2-nitro-1-butenyl)-benzene.
59. 2-Bromo-1-methylpropylbenzene.
60. (3-Bromo-1-methylpropyl)-benzene.
61. 1-(3-Azido-2-methylpropenyl)-2,4-dinitrobenzene.
62. 2-(2,4-Dinitrophenoxy)-1,3-dimethoxybenzene.
63. 4,4-(Dichloro-3,3-difluoro-1-cyclobuten-1-yl) benzene.
64. 2,6-Dibromo-3,4,5-trichlorophenol.
65. 1-(*p*-*tert*-Butylphenoxy)-4-(*p*-phenoxyphenoxy)-benzene.
66. 3-Methyl-1-phenylhexanol-3.
67. Thiophenol; 2-oxy-5-chlorine.
68. 1-Amino-1,2-diphenyldecanol-2.
69. 3,5-Diiodo-2-propoxybenzaldehyde.
70. Triphenyl-1,2,3-hexanedione-1,5.
71. 2-Amino-5-nitro-*m*-toluic acid.
72. 2,7-Bis(*p*-chlorophenyl)-4-octene-3,3,4,5,6,6-hexacarbo-
nitrile.
73. N-Benzyl- α,α,α -triphenyl-*p*-toluidine.
74. N⁴-(2-Chloro-4,6-dinitrophenyl)-2,4-diaminotoluene.
75. Anthranilic acid; 3-methyl-6-chlorine.
76. 3-Phenylphenoxyacetic acid.
77. 1-Vinyl-2-phenylnaphthalene.
78. 1-Bromo-4-(6-methoxynaphthyl-2)-3-methylhexanone-2.
79. 2-*sec*-Butyl-3-ethylnaphthalene.
80. 2-Oxy-4-methoxybenzophenone.
81. 4-Oxy-2'-methoxybenzophenone.
82. 2,2'-Diamino-4-nitrodiphenyl.
83. N¹-Phenyl-4-nitrophenylenediamine-(1,2).
84. 1,4,4a,5,8,8a,9,9a,10,10a Decahydro-1,4:5,8-dimetha-
noanthracene.
85. 1,2,3,4,5,6,7,8,9,10 Decahydro-1,4:5,8-dimethanoanth-
racene.
86. 1,2,3,4,5,8,8a,9,10,10a-Decahydro-1,4:5,8-dimethano-
anthracene.
87. Dibenzo[a, c]anthracene.
88. Dibenzo[b, g]phenanthrene.
89. Dicyclopenta[a, f]naphthalene.
90. Propanone-1; 2-bromo-1(thienyl-2-).
91. 3a,4,7,7a-Tetrahydro-4,7-ethanoisindole.
92. 9-Acetyl-1,4,5,8-tetrahydronaphthalene-4a,8a-imine.

93. Dibenzo[f,h] pyrrolo[1,2-b] isoquinoline.
94. 1H-Dibenzo [de,g] quinoline.
95. Naphtho[1,2-d]thiazole.
96. 1,5-Diazabicyclo [3.3.1] nonane.
97. 2-Acetyl-3-ethyl-4-phenyl-1, 2-diazabicyclo [2.2.2] octane.
98. 2,6,7-Trioxa-1-phosphabicyclo [2.2.2] octane.
99. 1-Bromoethyl-thienyl-2-ketone.
100. Naphtho [1,2-a] anthracene.
101. Naphtho [2,3-c] phenanthrene.
102. 4-Nitro-2-aminodiphenylamine.
103. *p*-Oxyphenyl-*o*-methoxyphenylketone.
104. Phenyl(4-methoxy-2-oxyphenyl)-ketone.
105. 2-Ethyl-3(1-methopropyl)naphthalene.
106. Methyl-ethyl-(3-ethylnaphthyl-2)methane.
107. 6-Methoxy-2(4-bromo-2-methyl-1-ethyl-3-oxobutyl)-naphthalene.
108. 6-Chloro-2-amino-3-methylbenzoic acid.
109. Methyl-propyl- β -phenylethylcarbinol.
110. α -Acetamido- β -ketoadipic acid.
111. 3-Methoxypropylamine.
112. 3-Chlorohexene-3-dinitrile-1,6.
113. Propionylpyrrolacemic acid.
114. Hexanedion-2,4-ic-1-acid.
115. α,γ -Dioxocapronic acid.
116. 2-Oxy-3, 3-dimethylbutyric acid.
117. β,β,β -Trimethylactic acid.
118. 2,2-Dimethylbutanol-3-ic-4-acid.
119. 1-Chloro-2(chloromethyl) butanol-3-ic-4-acid.
120. 4-Chloro-2-oxy-3-chloromethylbutyric acid.
121. γ -Chloro- α -oxy- β -chloromethylbutyric acid.
122. γ -Oxy- α -ethylbutyric acid.
123. Ethyl-(2-oxyethyl)-acetic acid.
124. 4-Oxy-2-ethylbutyric acid.
125. 4-Chloro-2-methylhexen-3-ol-1-one-5.
126. 2,6-Dimethyloctanol-2-al-8.
127. 2-Ethyl-2-hexenoic acid.
128. 2-Ethyl-3-propylacrylic acid.
129. 2-Methoethylbuten-3-oic-1 acid.
130. Vinylisopropylacetic acid.
131. 2-Isopropylbuten-3-oic-1-acid.

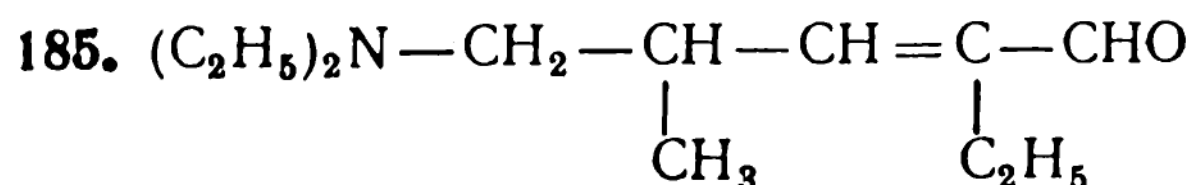
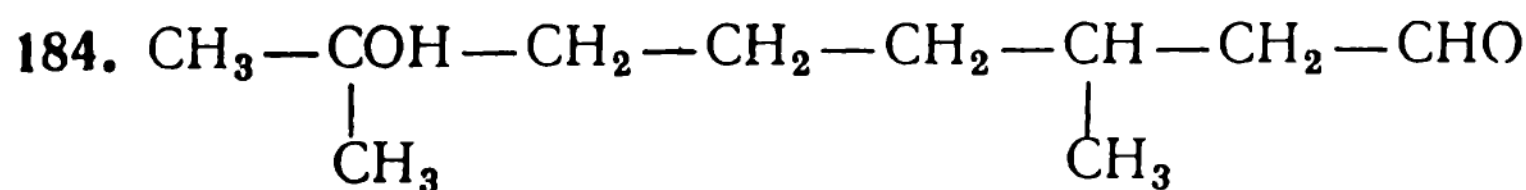
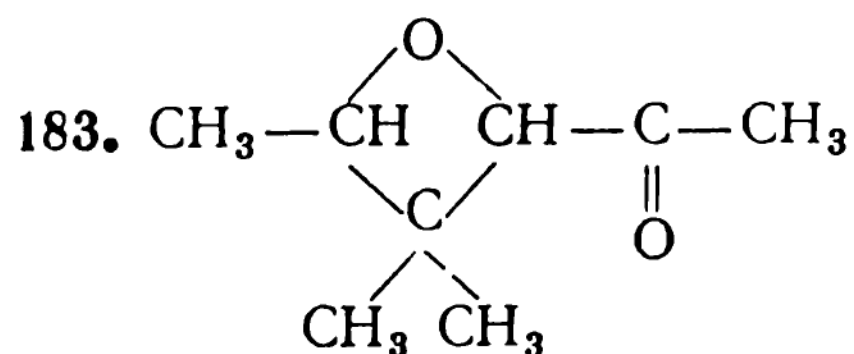
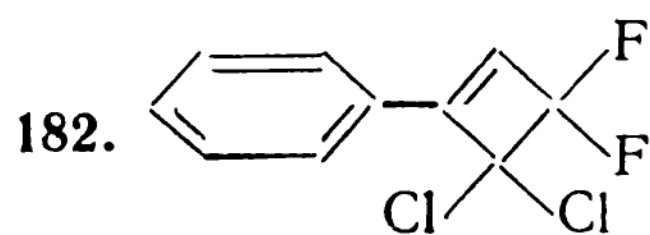
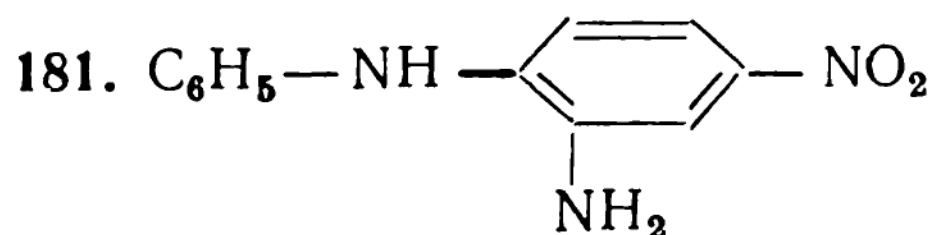
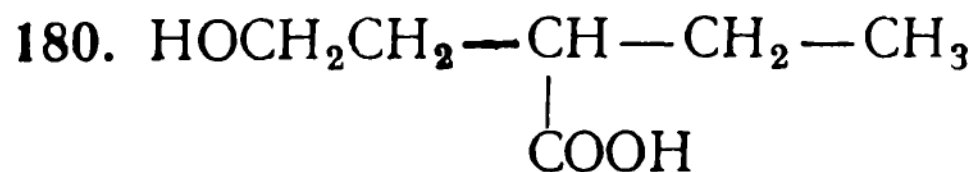
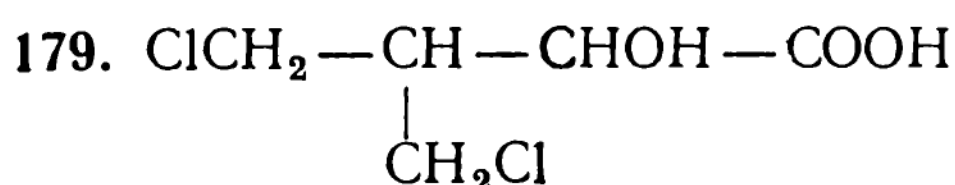
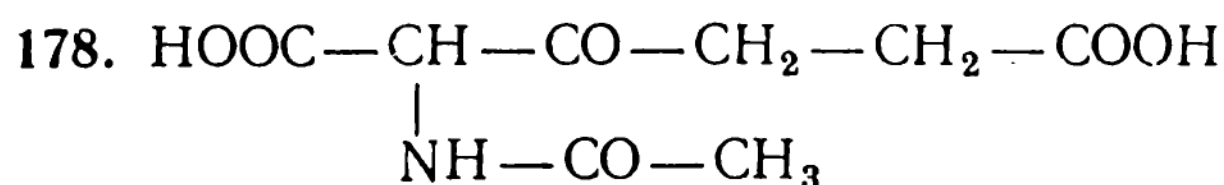
132. 2-Methyl-2-propylvaleric acid.
133. α, α -Dipropylpropionic acid.
134. 4-Methylheptanecarboxylic-4 acid.
135. 4-Carboxy-4-methylheptane.
136. 4-Carboxyheptane.
137. Dipropylacetic acid.
138. 2-Propylvaleric acid.
139. 4-Methylpentanecarboxylic-1 acid.
140. 5-Methylcapronic acid.
141. Isopentylacetic acid.
142. 1,5-Diaminohexane.
143. 1-Methylpentamethylenediamine.¹
144. 4-Acetylhexen-1-one-5.
145. 3-Allylpentanedione-2,4.
146. 2-Methylhexen-3-one-5.
147. 2-Methylpentanone-4.
148. Methylisobutylketone.
149. 2,6-Dimethyloctadien-2,6-al-8.
150. Methyl- α (-methylpropenyl)-ketone.
151. 3-Methylpenten-3-one-2.
152. 2-Methyl-2-ethylpenten-4-al-1.
153. 2-Methylpentanal-5.
154. γ -Methylvaleraldehyde.
155. Isobutylacetic aldehyde.
156. 2,4,4-Trimethylpenten-2-ol-5.
157. Vinylamylcarbinol.
158. 3-Methylolpentene-2.
159. (1-Ethylpropenyl) carbinol.
160. 3-Methylolheptanol-4.
161. Ethyl-*sec*-butylcarbinol.
162. 3-Methylhexanol-4.
163. Neopentyl chloride.
164. 3-Chloro-2-methylbutane.
165. *sec*-Isopentane chloride.
166. 3,4-Dipropylhexadien-1,3-yne-5.
167. α -Ethenyl- β -ethynyl- α, β -dipropylethylene.
168. α -Methyl- β -*sec*-butylethylene.
169. 3-Methylhexene-4.

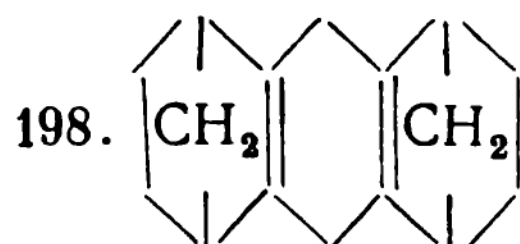
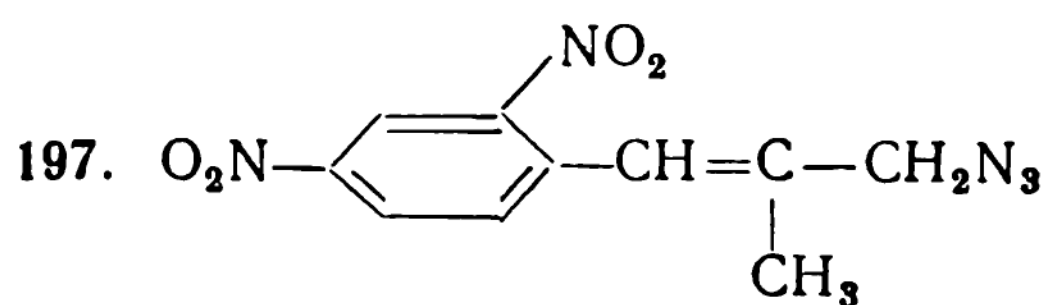
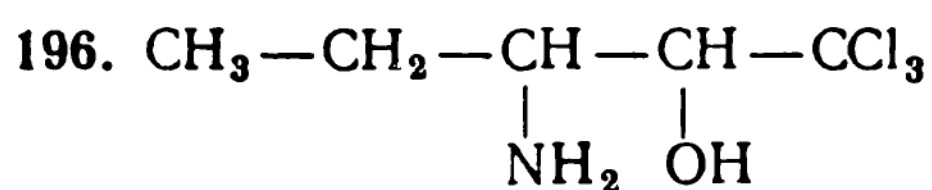
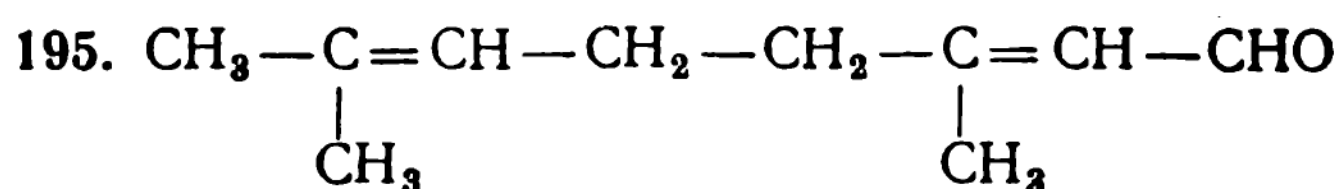
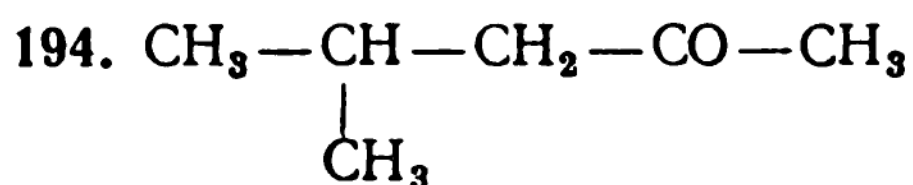
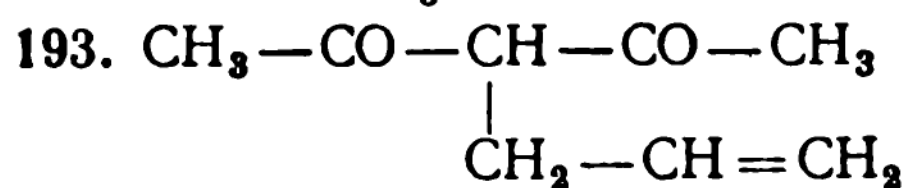
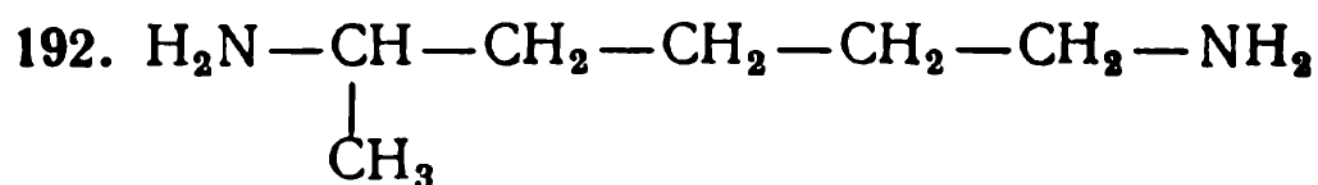
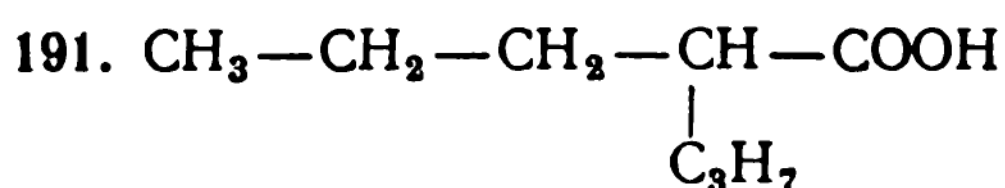
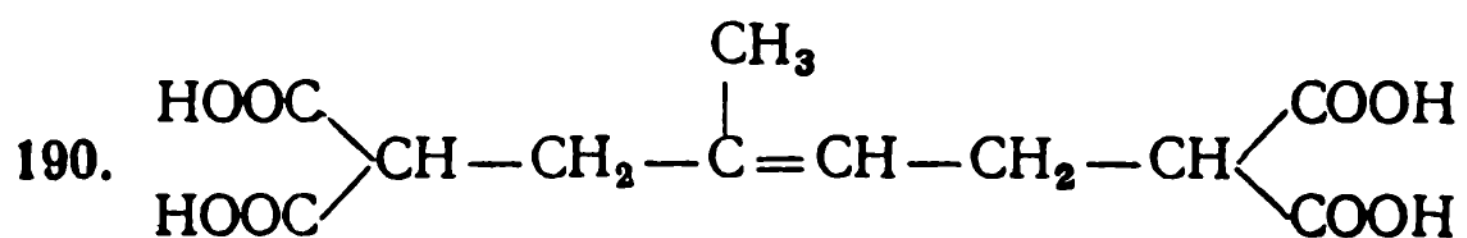
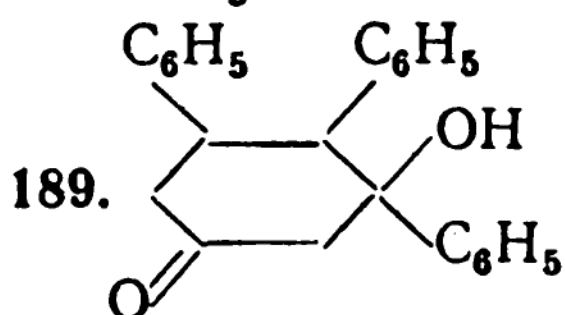
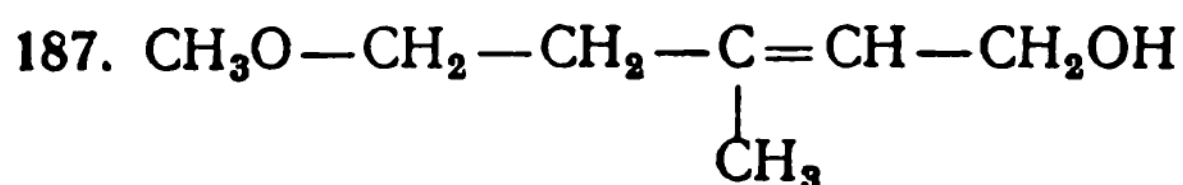
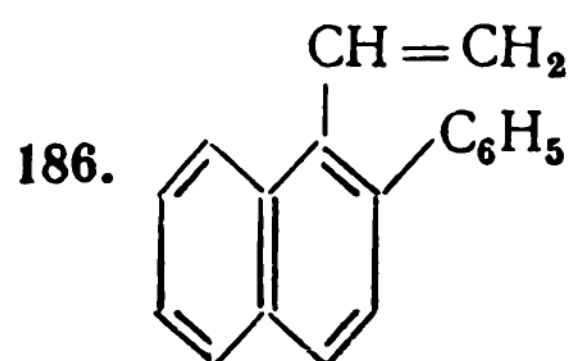
¹ This name taken from the literature conforms, strictly speaking, to one of nomenclature rules, but a formula can be written from it.

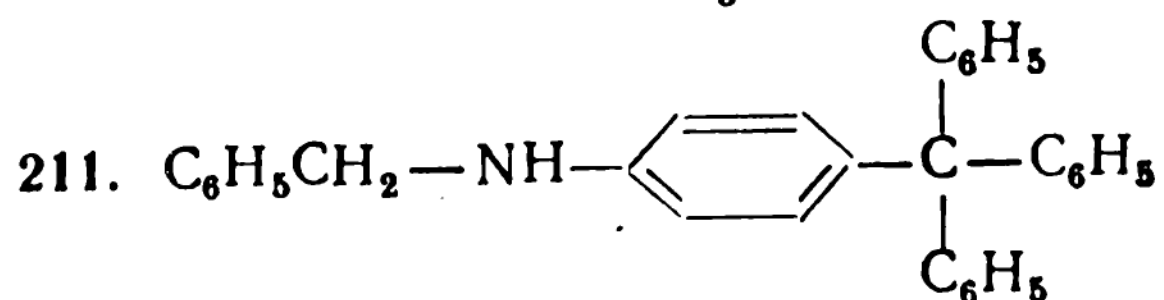
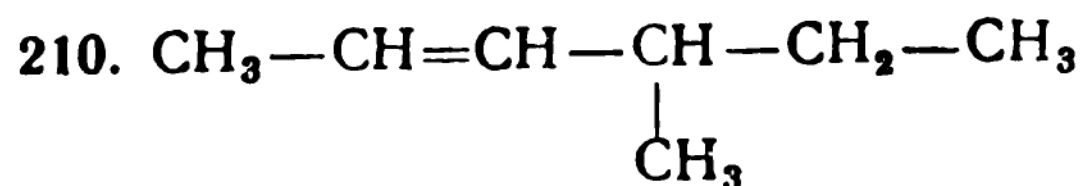
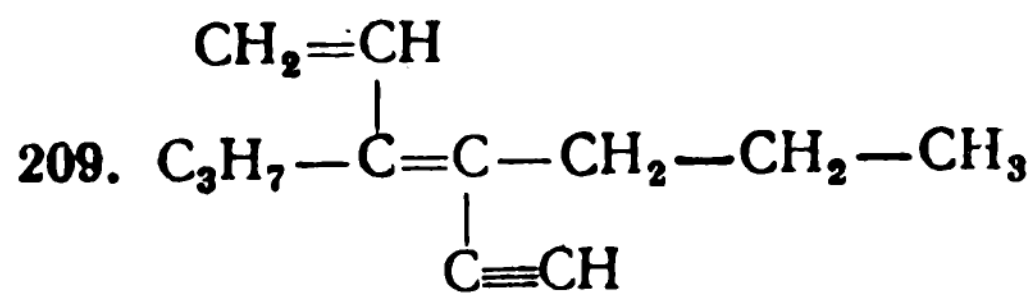
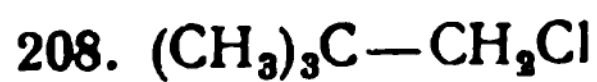
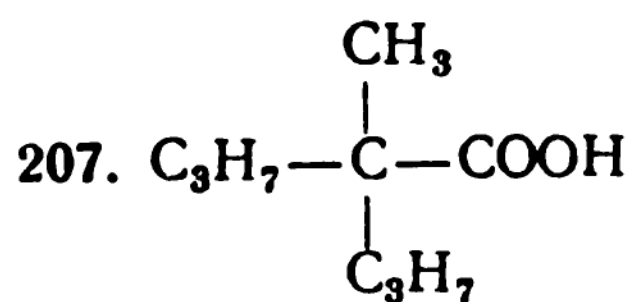
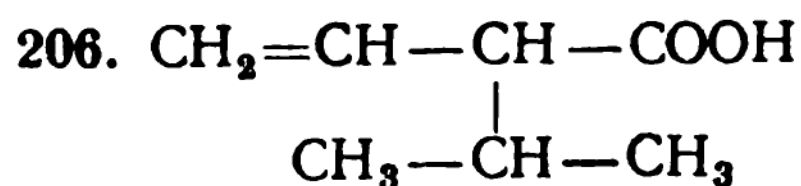
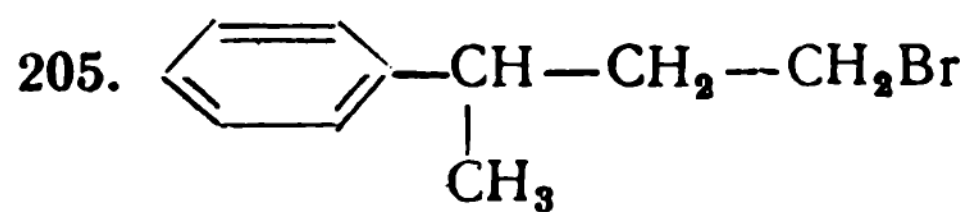
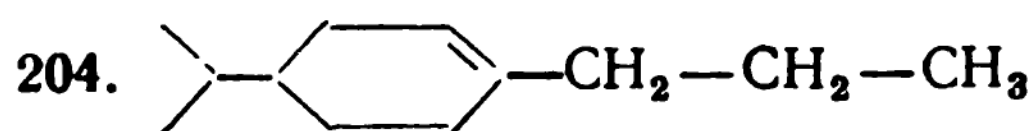
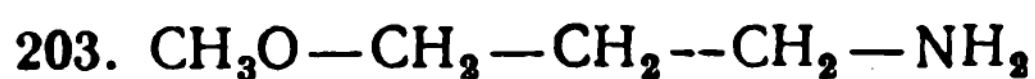
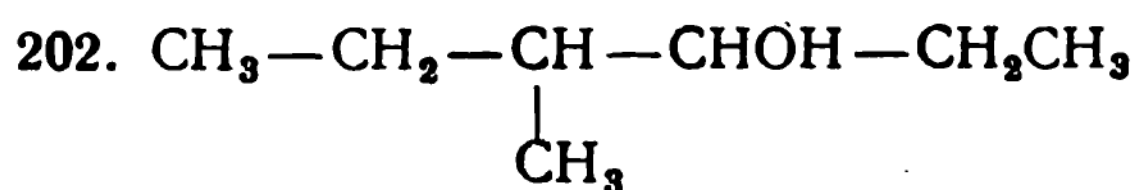
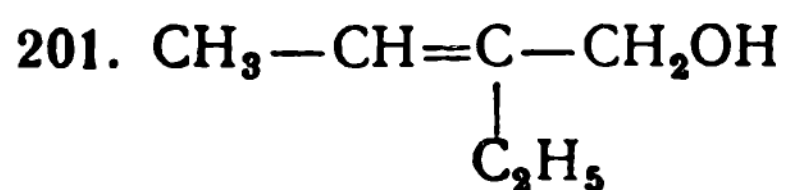
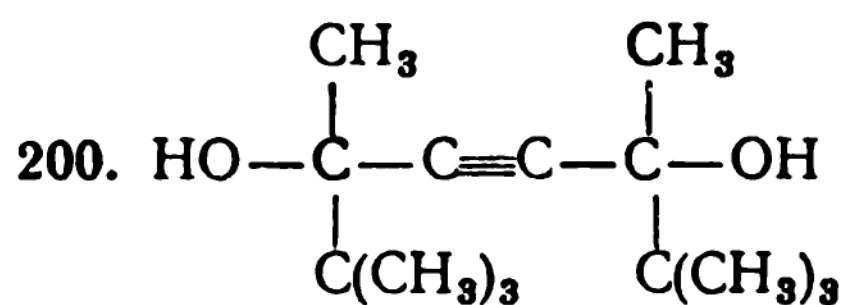
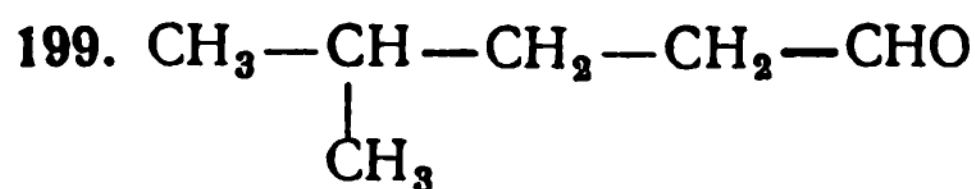
170. 2,2-Dimethylpentene-4.
 171. Neopentylethylene.
 172. 3-Methylhexadiene-1,5.
 173. Trimethylneopentylmethane.
 174. 2,2,4,4-Tetramethylpentane.
 175. Methylisopropylisobutylmethane.
 176. 5-Methoethyl-4-propyloctane.
 177. Propyl-isopropyl-(1-propylbutyl)methane.

Note: In most literature sources the locant 1 in names of compounds is omitted.

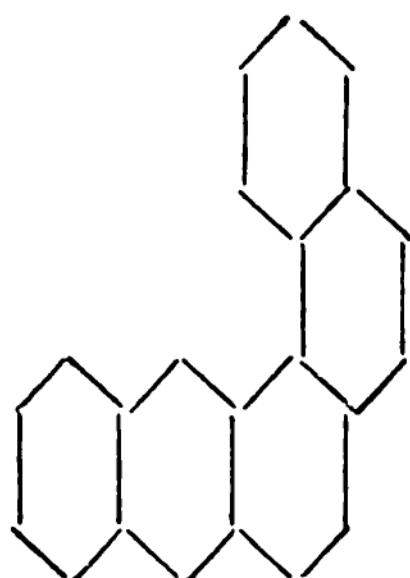
FORMULAS





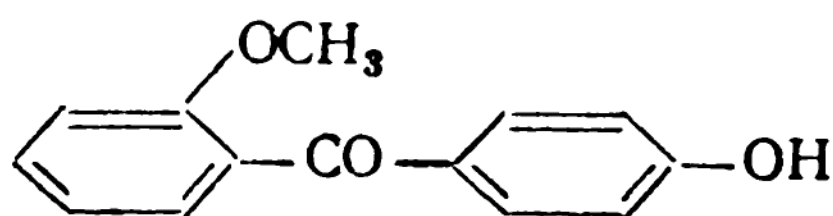


212.

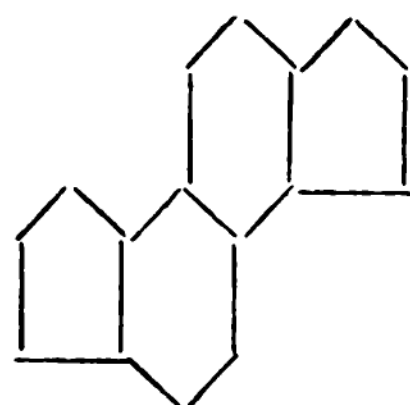


The completely aromatized structure is shown conditionally (double bonds not indicated)

213.



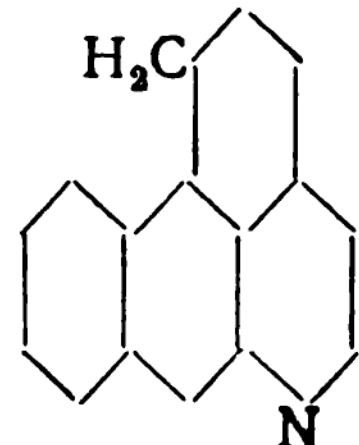
214.



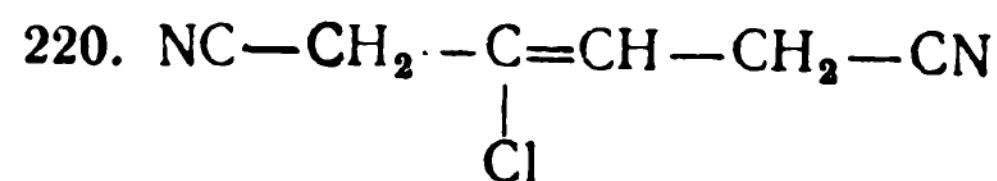
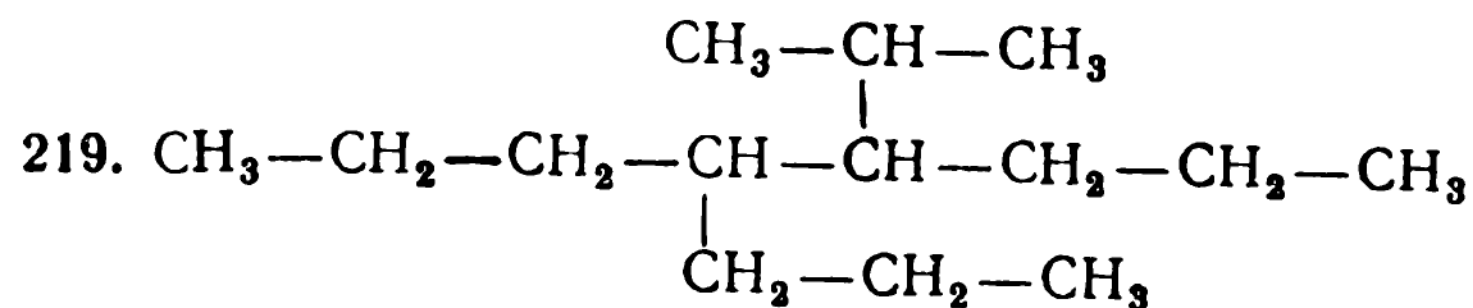
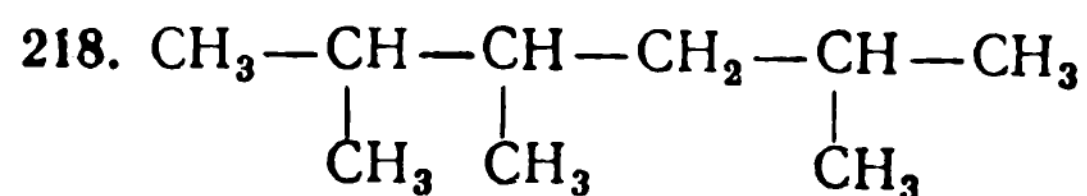
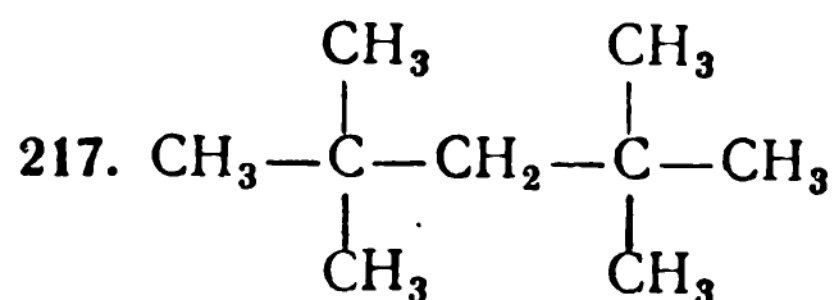
The completely aromatized structure is shown conditionally (double bonds not indicated)

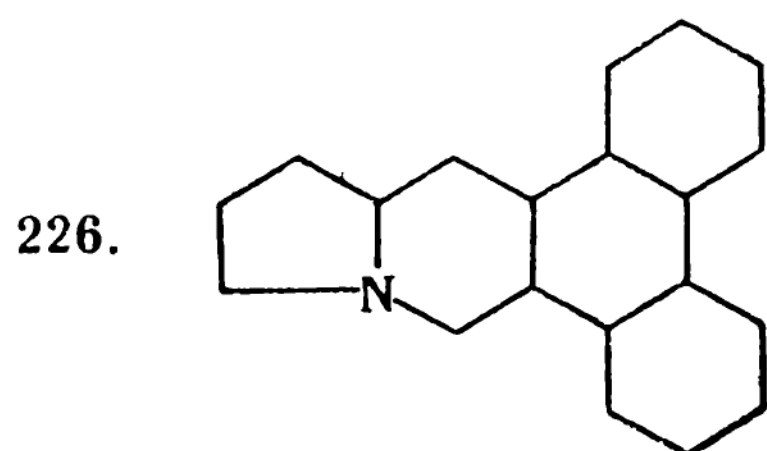
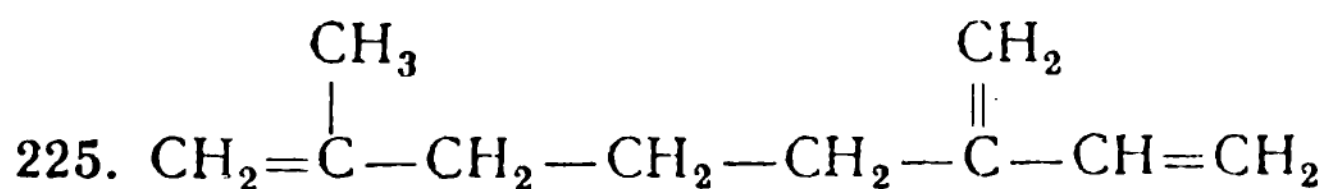
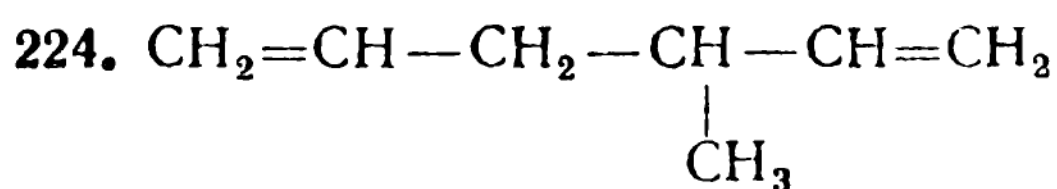
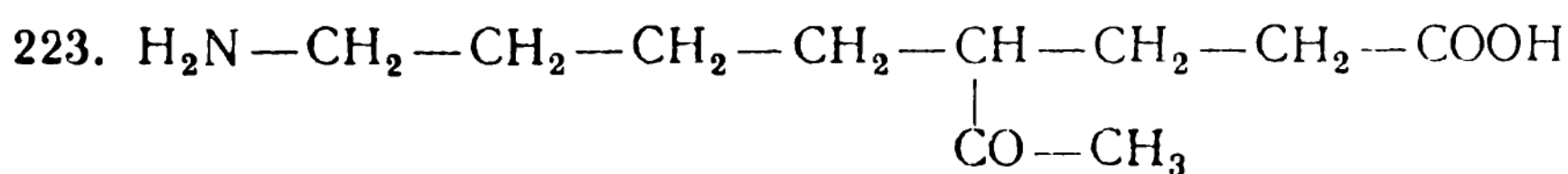
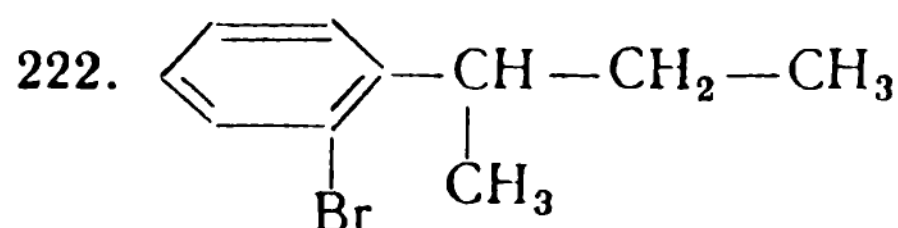
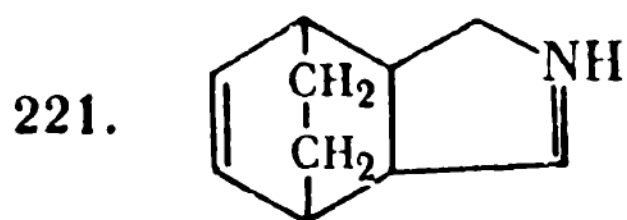
215. $(\text{CH}_3)_3\text{C}-\text{CH}_2-\text{CH}=\text{CH}_2$

216.

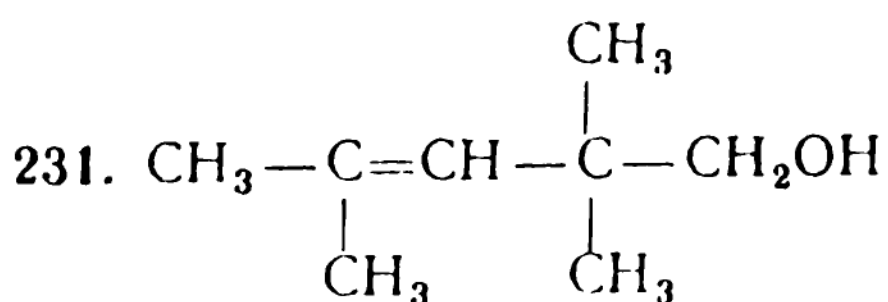
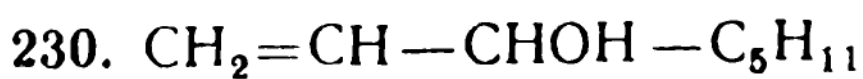
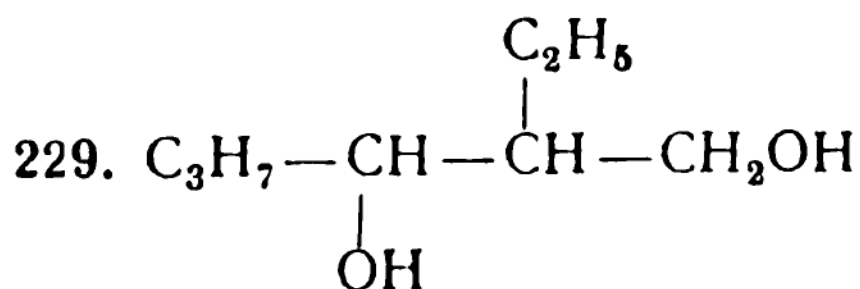
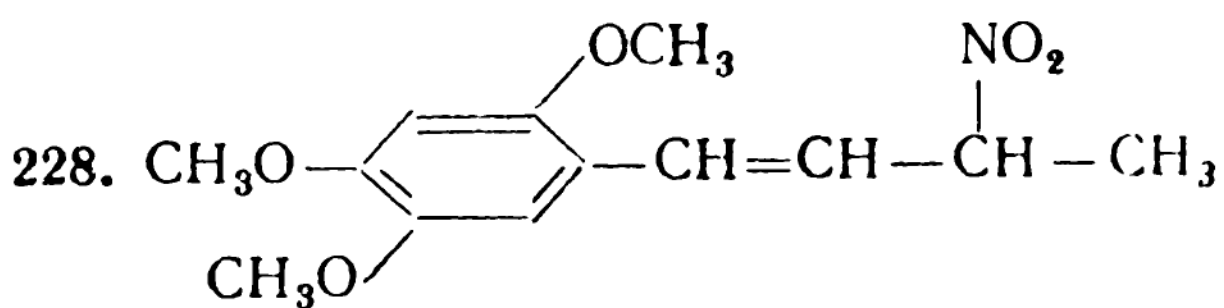
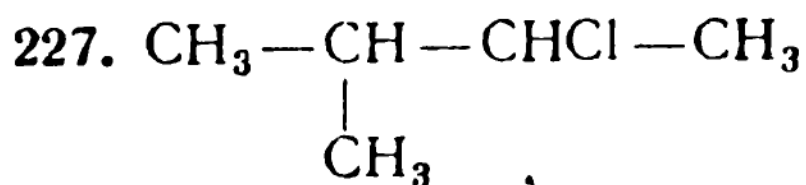


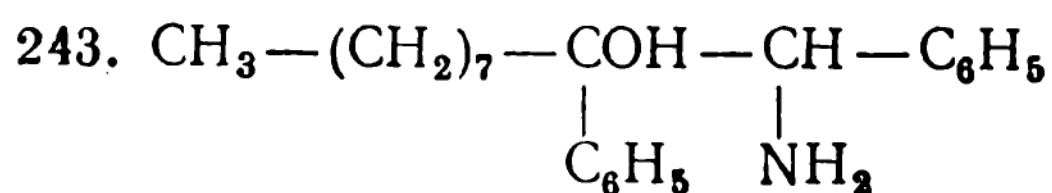
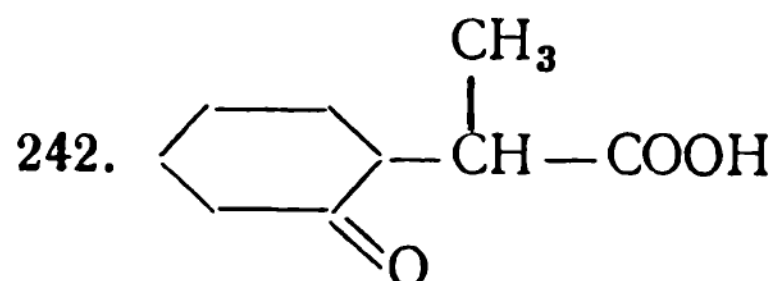
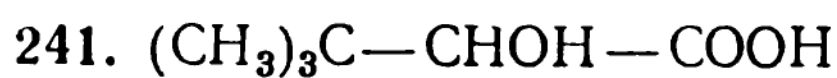
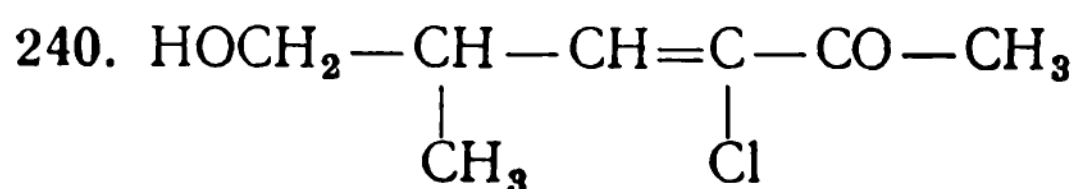
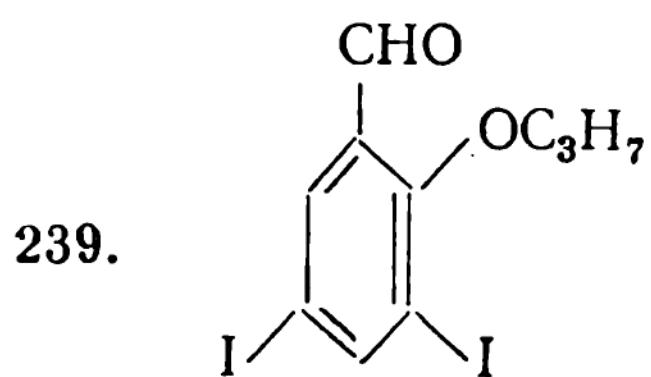
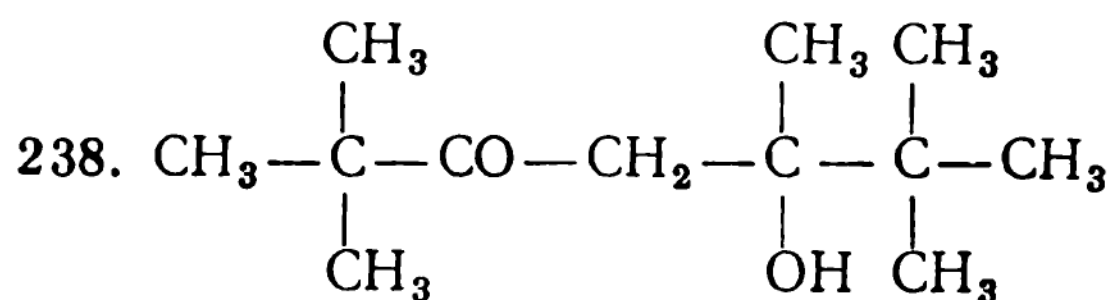
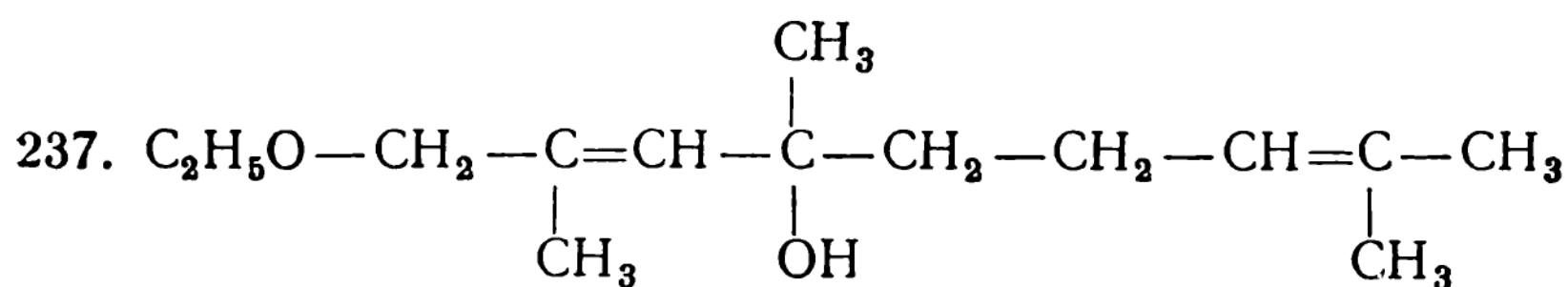
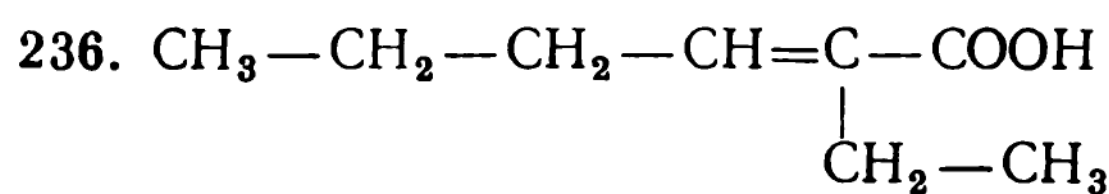
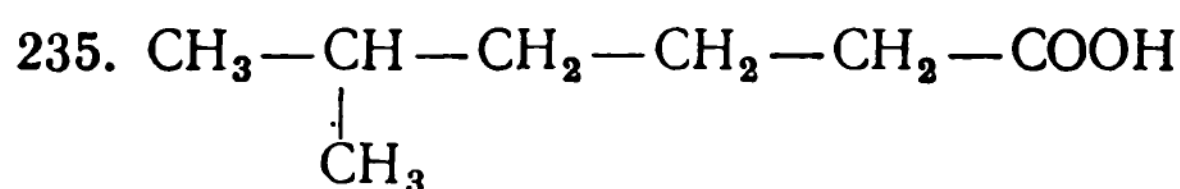
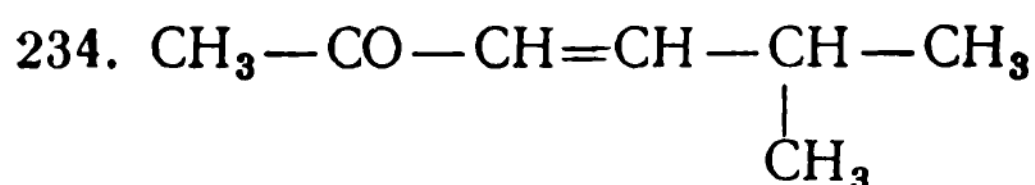
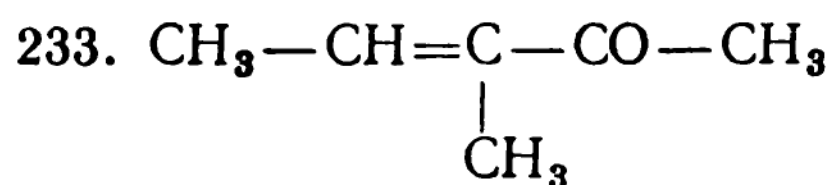
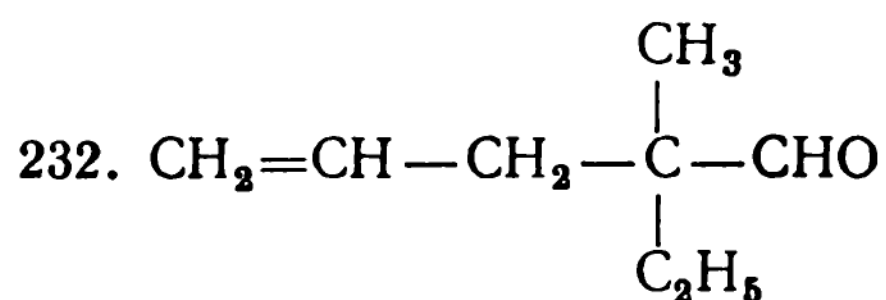
The completely aromatized structure is shown conditionally (double bonds not indicated)

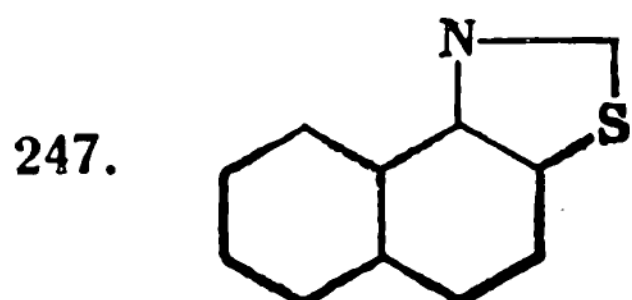
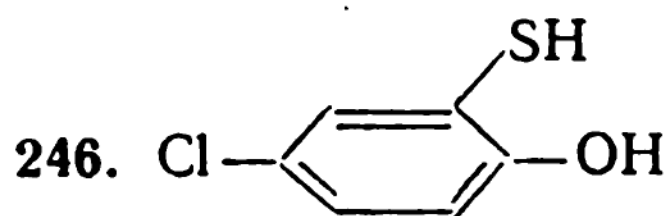
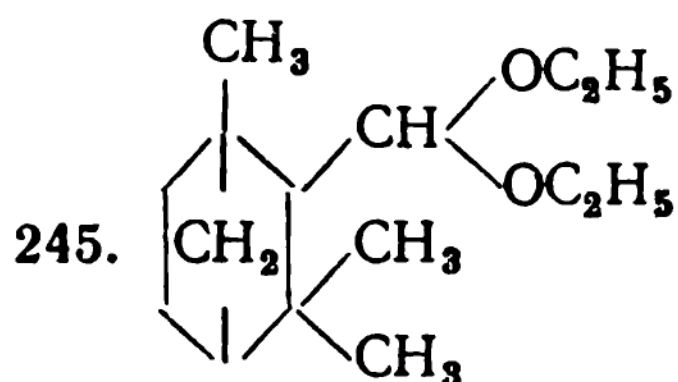
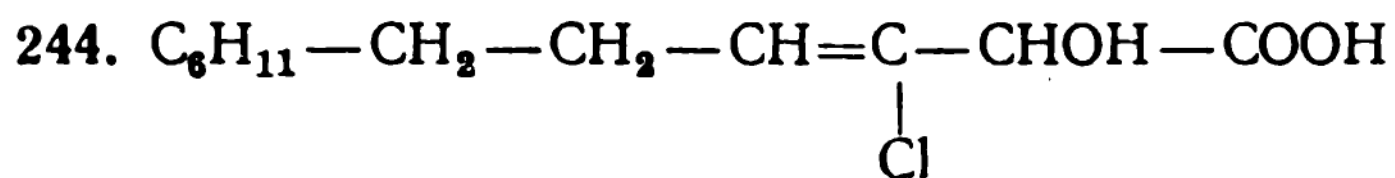




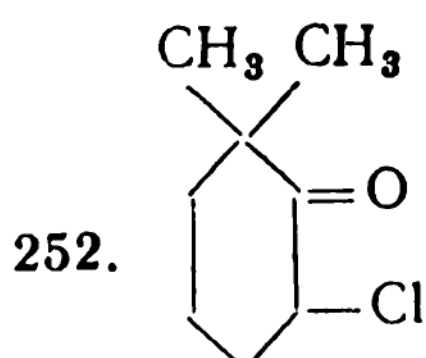
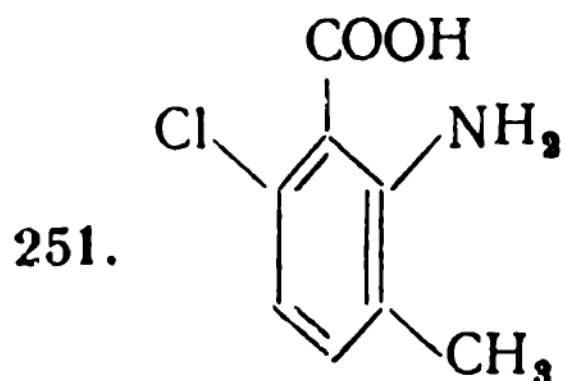
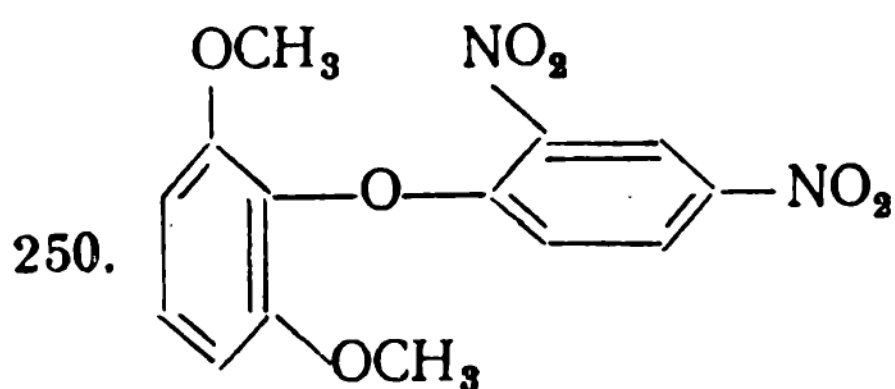
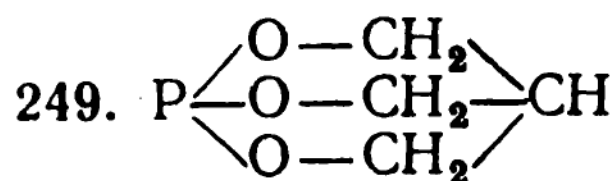
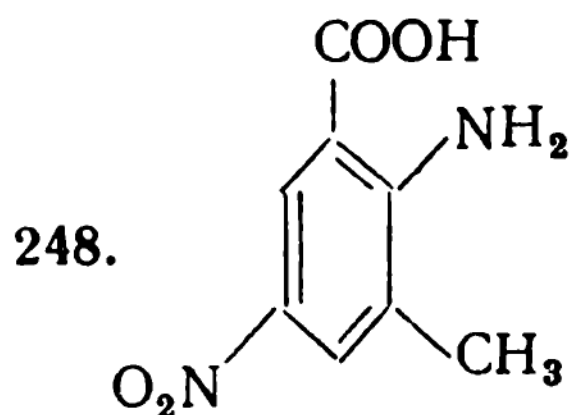
The completely aromatized structure is shown conditionally (double bonds not indicated)

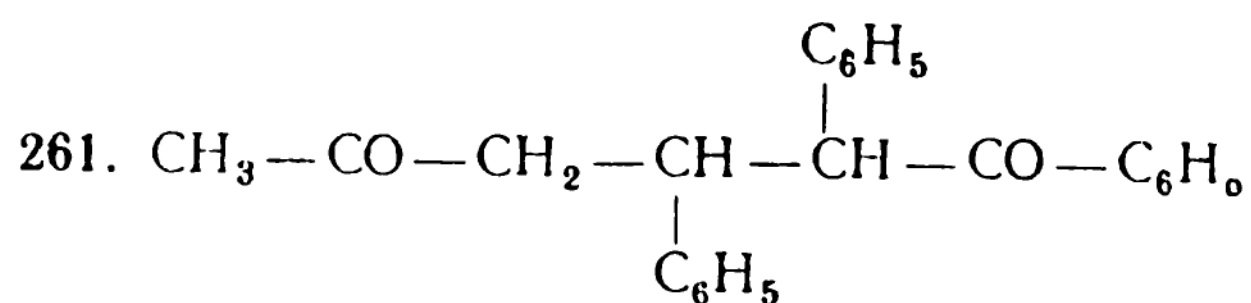
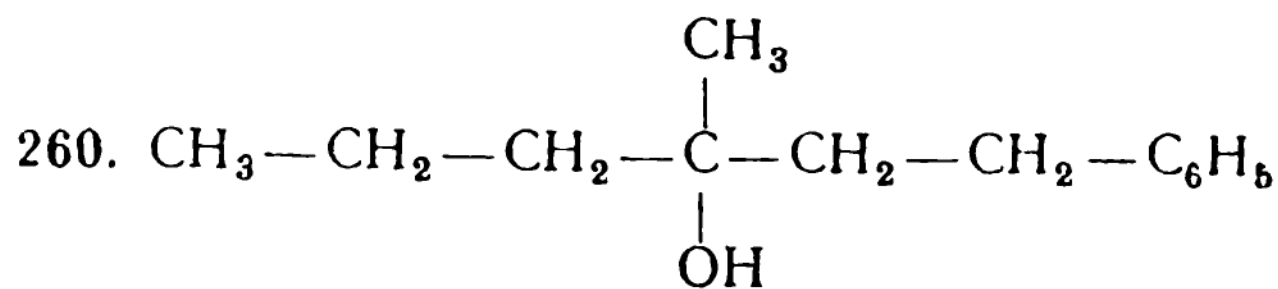
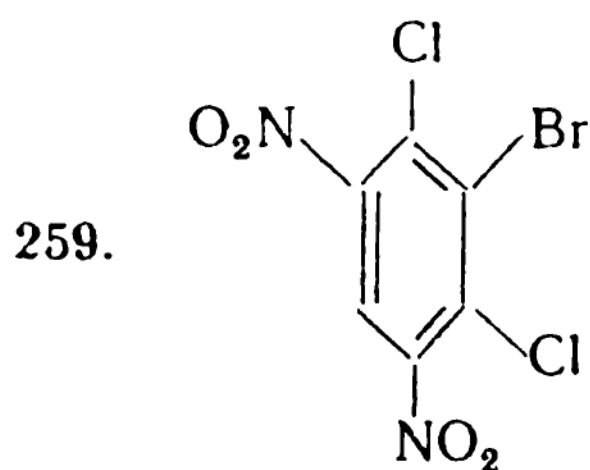
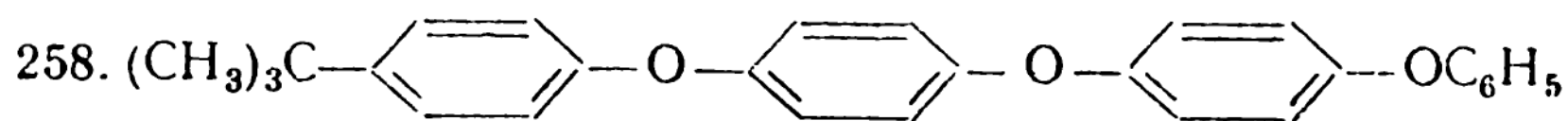
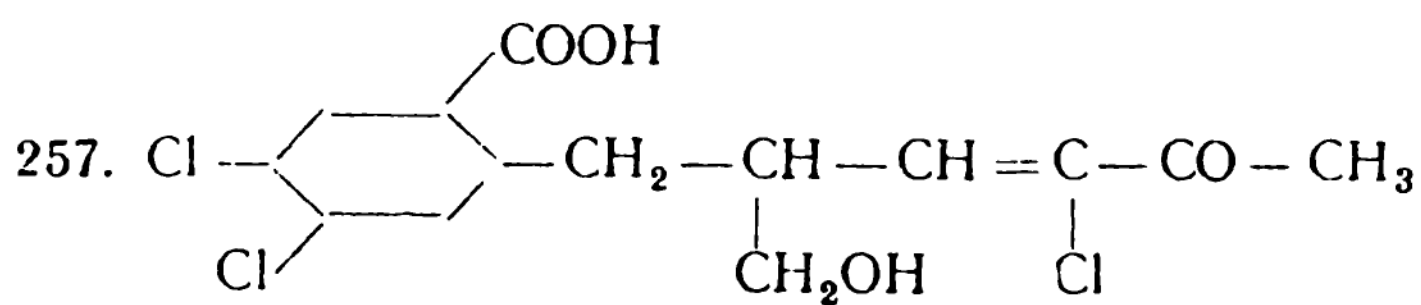
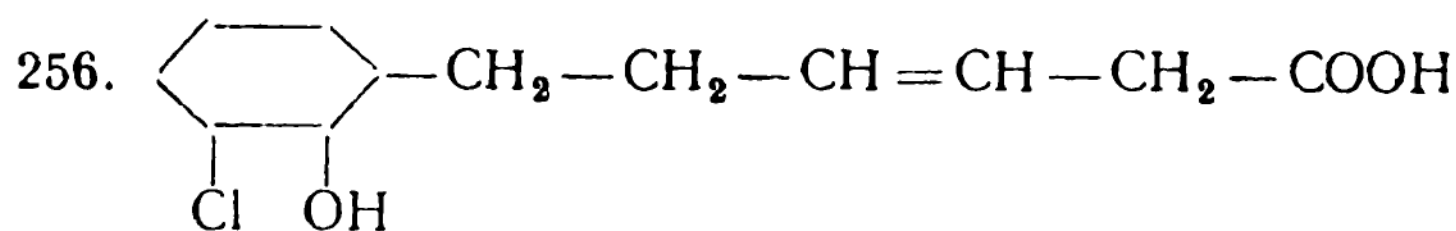
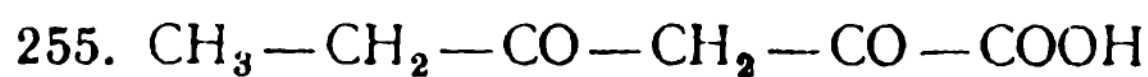
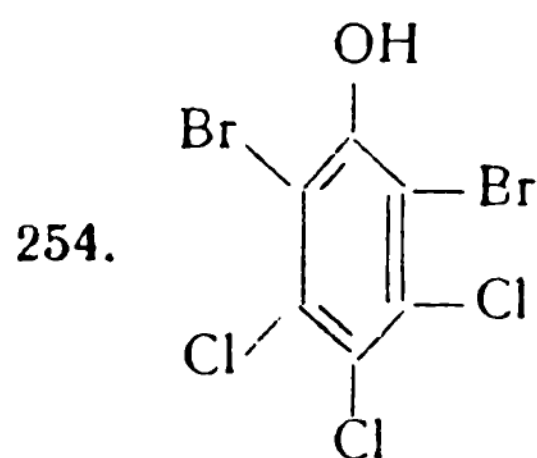
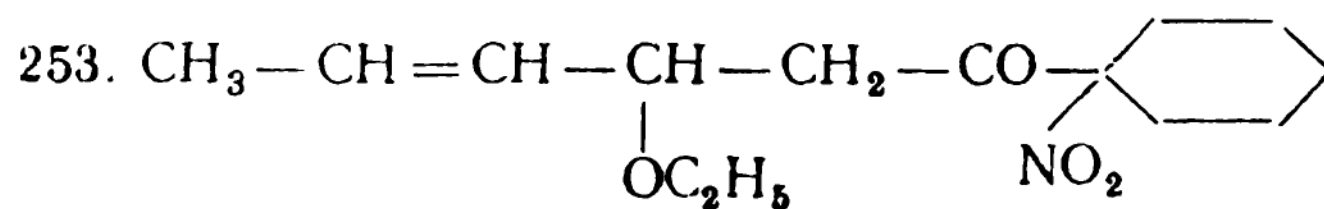


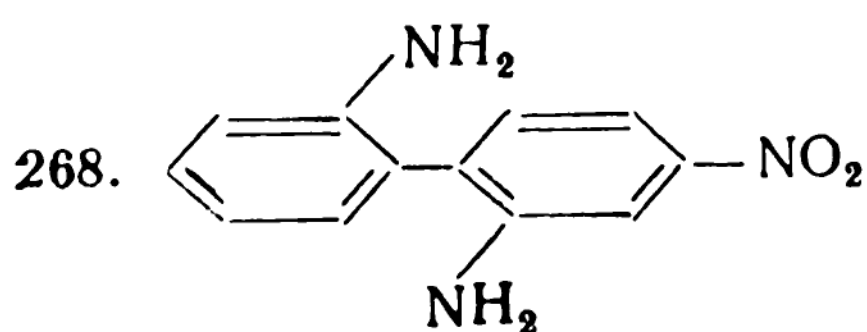
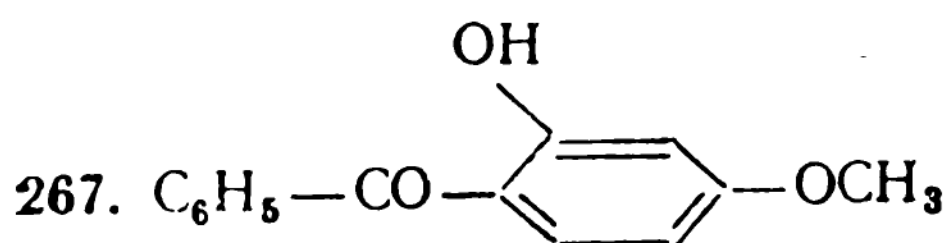
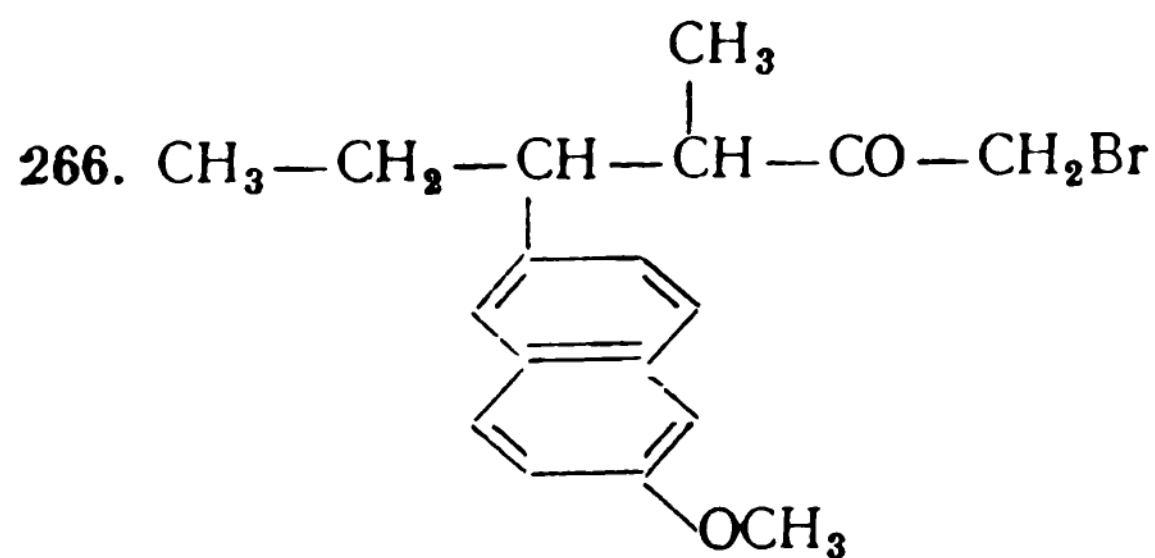
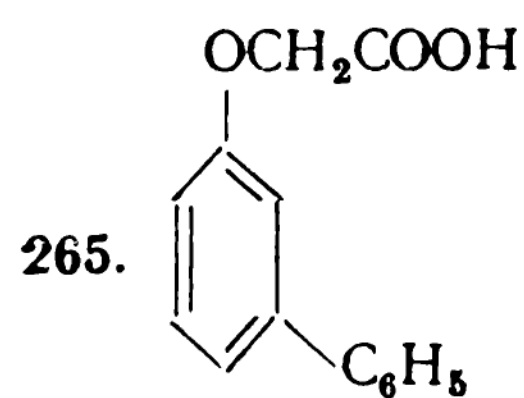
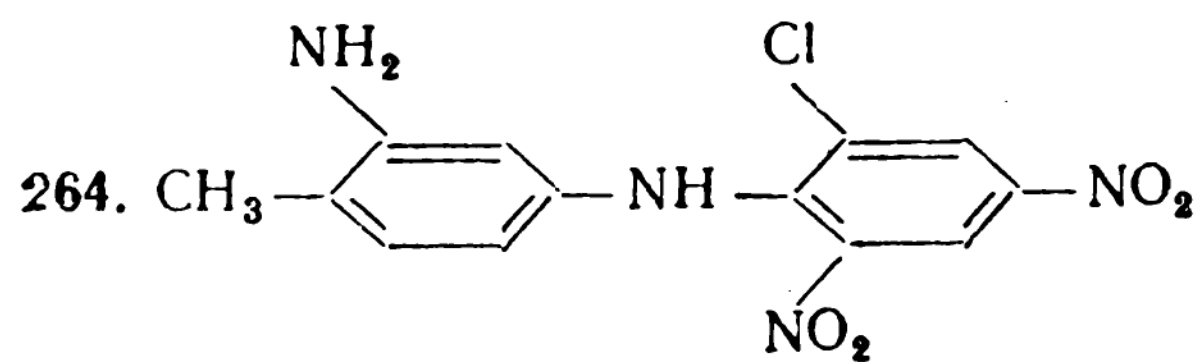
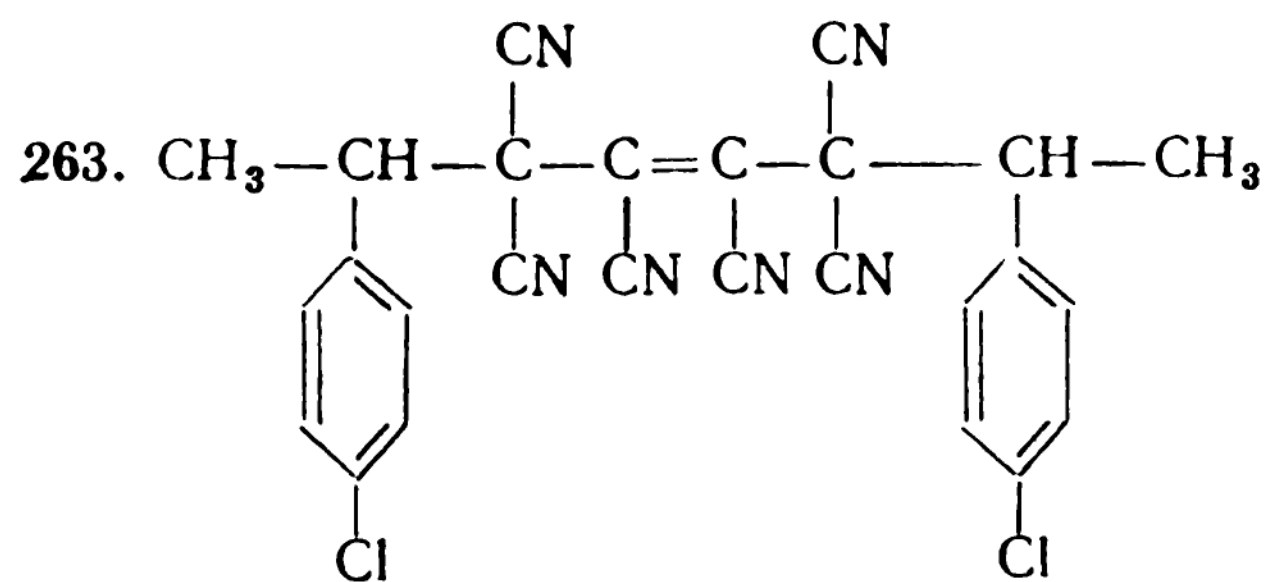
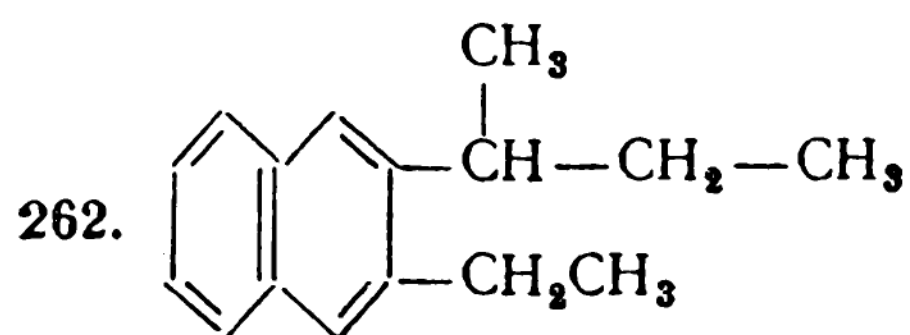


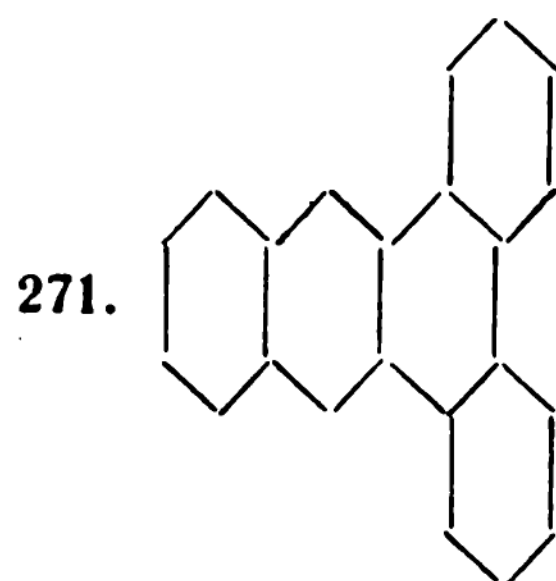
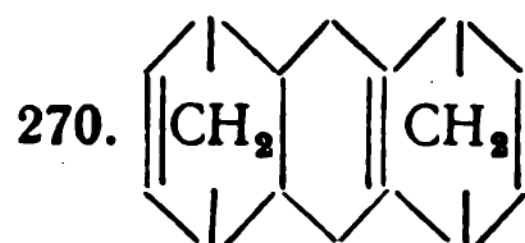
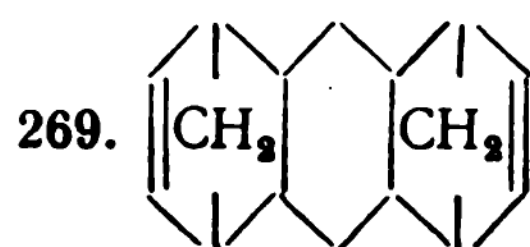


The completely aromatized structure is shown conditionally (double bonds not indicated)

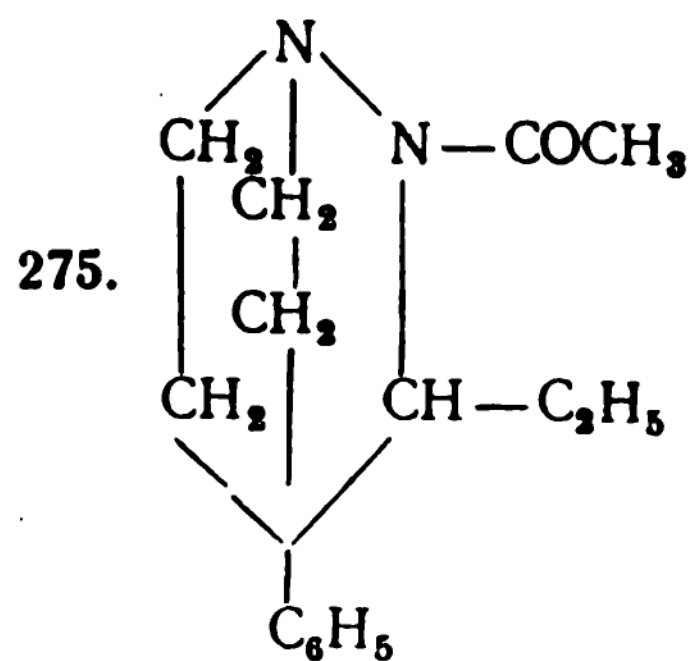
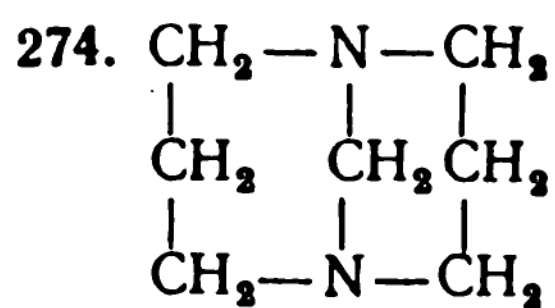
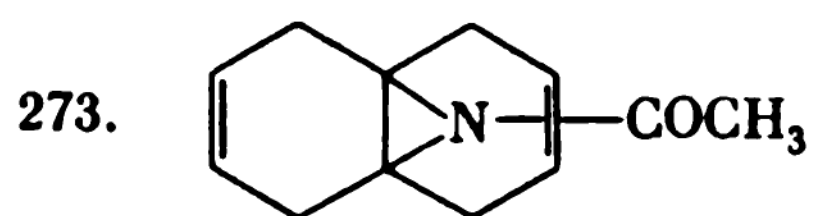
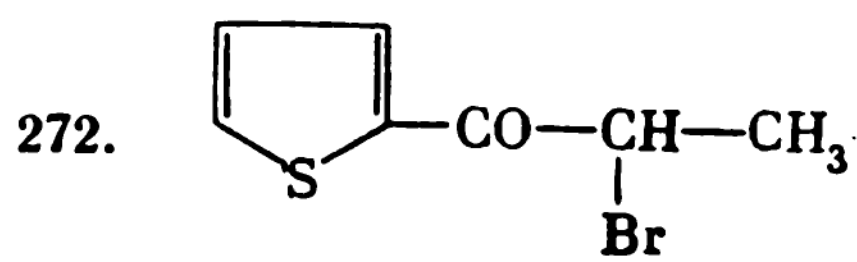








The completely aromatized structure is shown conditionally (double bonds not indicated)



Key for Search of Formulas from Names ¹

Name No.	0	1	2	3	4	5	6	7	8	9
0...		219	218	217	224	215	210	225	209	227
1...	208	202	229	201	230	231	200	199	232	233
2...	195	194	234	193	192	235	191	207	206	190
3...	188	236	187	237	184	185	238	183	240	180
4...	179	241	255	220	203	196	178	223	204	189
5...	252	242	253	244	256	257	245	259	228	222
6...	205	197	250	182	254	258	260	246	243	239
7...	261	248	263	211	264	251	265	186	266	262
8...	267	213	268	181	269	198	270	271	212	214
9...	272	221	273	226	216	247	274	275	249	272
10...	212	212	181	213	267	262	262	266	251	260
11...	178	203	220	255	255	255	241	241	241	179
12...	179	179	180	180	180	240	184	236	236	206
13...	206	206	207	207	207	207	191	191	191	235
14...	235	235	192	192	193	193	234	194	194	195
15...	233	233	232	199	199	199	231	230	201	201
16...	229	202	202	208	227	227	209	209	210	210
17...	215	215	224	217	217	218	219	219		

¹ This key is composed like a table of logarithms; in the first vertical column are placed numbers from 0 to 17 corresponding to the first two numerals of name numbers; the last figures of these numbers are put in the first line along the horizontal. The number of a formula corresponding to a given name number can be found at the intersection of the corresponding horizontal and vertical lines. For example, to the name under 124 there corresponds formula 180 (the horizontal 12... and the vertical 4 intersect at 180).

Key for Search of Names from Formulas¹

Formula No.	0	1	2	3	4	5	6	7	8	9
-------------	---	---	---	---	---	---	---	---	---	---

Name No.

17...									46 110	40 119-121
18...	39 122- -124	83 102	63	37	34 126	35	77	32	30	49
19...	29	26 136-138	24 142 143	23 144 145	21 147 148	20 149	45	61	85	17 153-155
20...	16	13 158 159	11 161 162	44 111	48	60	28 129-131	27 132-135	10 163	8 166 167
21...	6 168 169	73	88 100 101	81 103	89	5 170 171	94	3 173 174	2 175	1 176 177

Formula No.	0	1	2	3	4	5	6	7	8	9
22...	43 112	91	59	47	4 172	7	93	9 164 165	58	12 160
23...	14 157	15 156	18 152	19 150 151	22 146	25 139-141	31 127 128	33	36	69
24...	38 125	41 116-118	51	68	53	56	67	95	71	98
25...	62	75 108	50	52	64	42 113-115	54	55	65	57
26...	66 109	70	79 105 106	72	74	76	78 107	80 104	82	84
27...	86	87	90 99	92	96	97				

' This key is composed like the previous one, but this time names are to be found from formula numbers.

CHAPTER 2

FREE-RADICAL REACTIONS

INTRODUCTION

Free-radical, or simply radical, reactions of substitution belong in the category of transformations most characteristic of paraffin hydrocarbons. Such reactions are, as a rule, chain reactions induced by the action of various initiators. The role of an initiator can be played by a physical influence (heat, light, radioactive radiation) or by chemical substances capable of decomposing readily to form free radicals [for instance, benzoyl peroxide, $\text{C}_6\text{H}_5\text{CO}-\text{O}-\text{O}-\text{COC}_6\text{H}_5$; α, α' -azobis-isobutyronitrile, $(\text{CH}_3)_2\text{C}(\text{CN})-\text{N}=\text{N}-\text{C}(\text{CN})(\text{CH}_3)_2$; cumene hydroperoxide, $\text{C}_6\text{H}_5-\text{C}(\text{CH}_3)_2-\text{OOH}$].

Radical reactions are slowed down by addition of inhibitors, substances that bind free radicals, thereby breaking the chain. The inhibitors most widely used are oxygen, hydroquinone, quinones, aromatic nitro derivatives, and some of the aromatic amines and alkyl phenols.

In radical reactions, the reagent primarily attacks those bonds which are most easily breakable, i.e., possessing a lower energy. The energies required to break up various types of C—H bonds are as follows:

CH_3-H		102 kcal/mole
$\text{CH}_3-\text{CH}_2-\text{H}$		98 kcal/mole
$(\text{CH}_3)_2\text{CH}-\text{H}$		94 kcal/mole
$\text{C}_6\text{H}_5-\text{H}$		102 kcal/mole
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{H}$		77 kcal/mole
$\text{C}_6\text{H}_5-\text{CH}_2-\text{H}$		75 kcal/mole

The magnitude of this energy is usually the lower (and hence the probability of a corresponding radical being formed is the higher), the greater the possibility of delocalization of a free electron.

The selectivity of radical reactions is generally the higher, the milder the conditions under which they are carried out

(for instance, the lower the temperature) and the lower the activity of the reagent.

For detailed information about radical reactions the reader is referred to the book *Organikum; organisch-chemisches Grundpraktikum*, Berlin, 1964.

Problems and Exercises

1. Arrange the following compounds in order of increasing ease of their dissociation into free radicals:

(a) 2,2,3,3-tetramethylbutane, hexaphenylethane, 1,1,2,2-tetraphenylethane, hexa-*p*-diphenylethane;

(b) hexaphenylethane, hexa-*p*-nitrophenylethane, 2,3-dimethyl-2,3-diphenylbutane.

2. When an organic compound decomposes on heating, the following radicals are formed: isopropyl, methyl, and *tert*-butyl. Arrange these radicals in order of increasing lifetime.

3. How could you account for the fact that the relative reactivity of C—H bonds at primary, secondary, and tertiary carbon atoms in a chlorination reaction at -50°C is expressed by the ratio 1 : 7.2 : 11.8 and at $+50^{\circ}\text{C}$ by the ratio 1 : 2.9 : 4.5?

4. The relative reactivity of α -, β -, and γ -hydrogen atoms in the radical chlorination of *n*-butyronitrile is 0.04 : 3.1 : 1. What is the ratio of the amounts of α -, β -, and γ -chloro-substituted nitriles in the chlorination products?

5. The relative reactivity of α -, β -, and γ -hydrogen atoms in the radical chlorination of *n*-butyric acid is 0.24 : 3.1 : 1. What is the percentage composition of the mixture of mono-chlorination products?

6. The relative reactivity of the primary, secondary, and tertiary C—H bonds in a radical bromination reaction is 1 : 32 : 1600. What is the percentage composition of the mixture of the products of the radical monobromination of isopentane if the above reactivity of various C—H bonds is assumed for it?

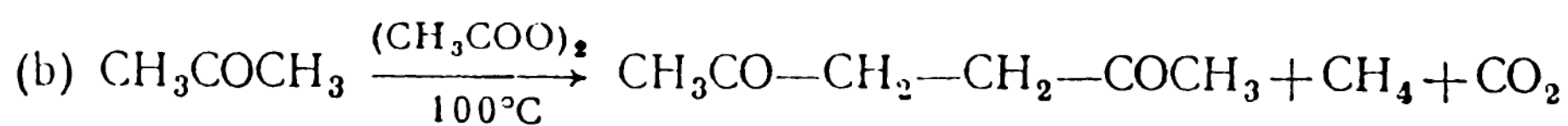
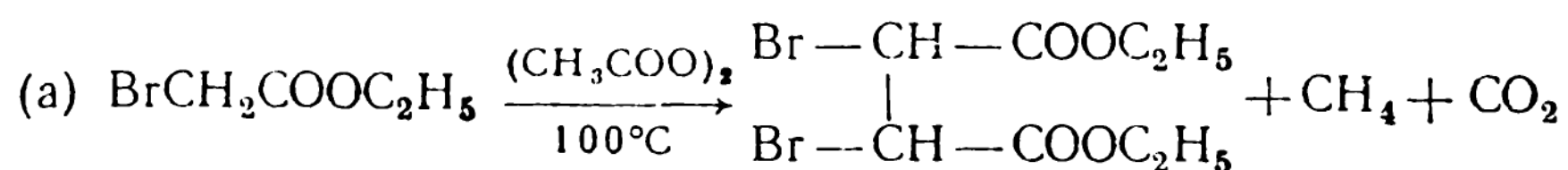
7. When isobutane is nitrated with nitric acid in a gaseous phase at 450°C , there are formed 65 per cent of a primary and 7 per cent of a tertiary nitro compound (the rest being the destruction products). What are the relative rates of

the substitution of the primary and tertiary hydrogens under these conditions? How can you explain the observed result?

8. The chlorination of isobutylene labelled with C^{14} at the methylene group and the subsequent ozonization resulted in the formation of formaldehyde and chloroacetone, the latter alone containing the tracer carbon. What conclusions can be made concerning the mechanism of the reaction if the reaction is not inhibited by oxygen?

9. α -Halogen-ethylbenzene is to be synthesized from ethylbenzene. By the action of what halogen and under what conditions can this reaction be carried out?

10. Suggest schemes for the mechanism of the following transformations:



11. Why is it better to prepare dihalides (bromides, chlorides) from alkenes in the dark?

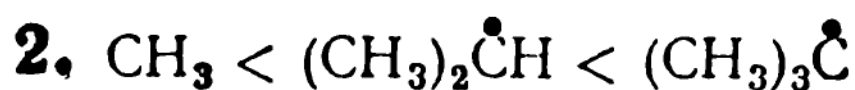
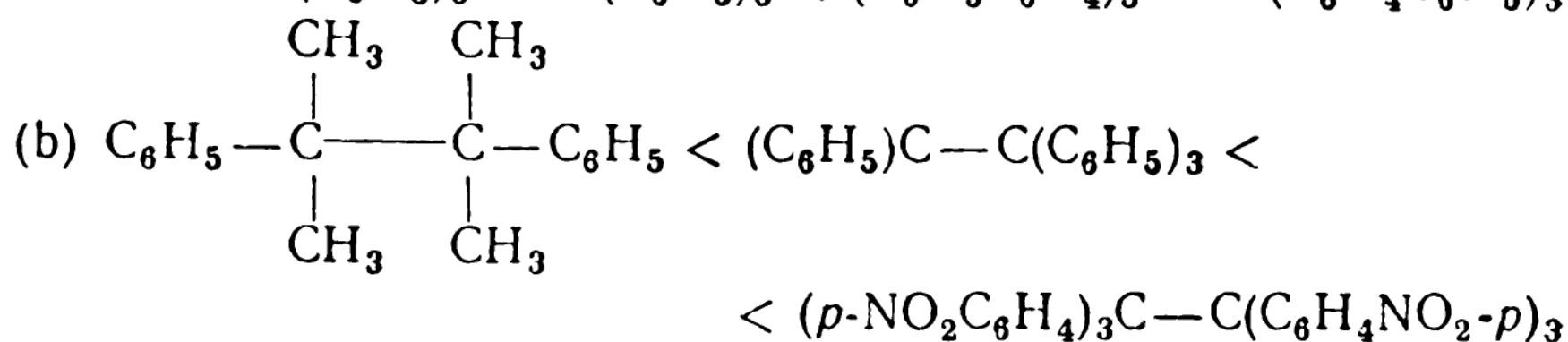
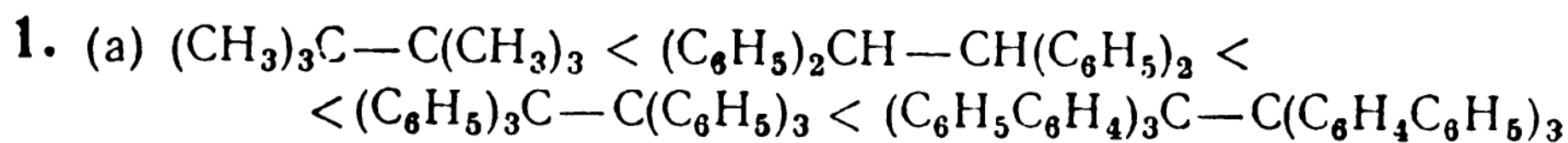
12. Solutions of tetraphenylhydrazine are colourless, but when heated they assume a green-brown colour which disappears on cooling; after cooling the original compound can be isolated. When equimolar quantities of tetraphenylhydrazine and hexaphenylethane are heated, a new compound having the composition $\text{C}_{31}\text{H}_{25}\text{N}$ is formed on cooling. How can these facts be accounted for?

13. Suggest a mechanism for the conversion of cumene into 2,3-dimethyl-2,3-diphenylbutane on heating in the presence of di-*tert*-butyl peroxide.

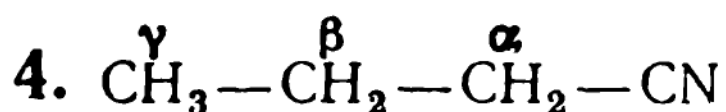
14. Write the scheme of the bromination of isopropylbenzene and *p*-chlorotoluene in the presence of benzoyl peroxide.

15. When a toluene solution of benzophenone (diphenyl ketone) was subjected to ultraviolet radiation, the following compounds were isolated: 1,1,2,2-tetraphenylethylene glycol, diphenylbenzylcarbinol, and 1,2-diphenylethane. Explain the mechanism of the formation of these compounds.

Answers



3. As the temperature rises the activity of the reagent (chlorine in this case) increases and, as a result, it becomes capable of breaking up not only bonds with the lowest energy ($\text{C}_{\text{tert}}-\text{H}$) but stronger bonds ($\text{C}_{\text{sec}}-\text{H}$, $\text{C}_{\text{pr}}-\text{H}$) as well. Therefore the selectivity of the reaction decreases, as a general rule, with rise of temperature.



The relative reactivity characterizes the relative reaction rate in terms of one bond of a corresponding type ($\text{C}-\text{H}$ in this particular case). To express it in terms of the ratio of reaction products one should additionally take into account the number of bonds of each type (3- γ , 2- β , and 2- α):

$$3 \times 1 : 2 \times 3.1 : 2 \times 0.04 = 3 : 6.2 : 0.08, \text{ i. e., about } 32\% \gamma, \\ 67\% \beta, \text{ and } 1\% \alpha$$

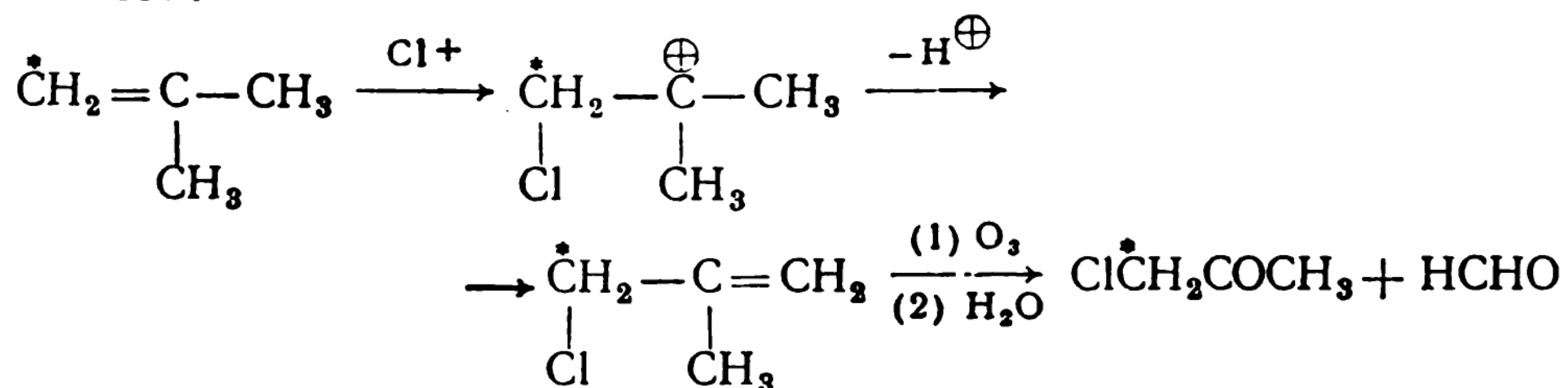
5. Assuming the sum $2 \times 0.24 + 2 \times 3.1 + 3 \times 1$ to be equal to 100 per cent, we calculate the percentage content of the monochlorination products: $\alpha = 5$ per cent, $\beta = 64$ per cent, $\gamma = 31$ per cent.

6. The compound $(\text{CH}_3)_2\text{CH}-\text{CH}_2-\text{CH}_3$ has one tertiary, two secondary and nine primary $\text{C}-\text{H}$ bonds. Taking into account the reactivity of these bonds (see the statement in Problem 6), one can easily calculate the ratio of the amounts of monobromination products ($9 \times 1 : 2 \times 32 : 1 \times 1600 = 9 : 64 : 1600$) and then the percentage composition of the mixture (0.6, 3.8 and 95.6 per cent, respectively).

7. With account taken of the $\text{C}-\text{H}$ bonds present the relative rate of replacement of the primary hydrogen is $65/9 \approx 7$,

and that of the tertiary hydrogen, $7/1 = 7$. The reaction is not selective because of the high temperature.

8. The reaction proceeds via the step of addition of $\text{Cl}^\oplus$ with the subsequent removal of the proton from the cation formed:

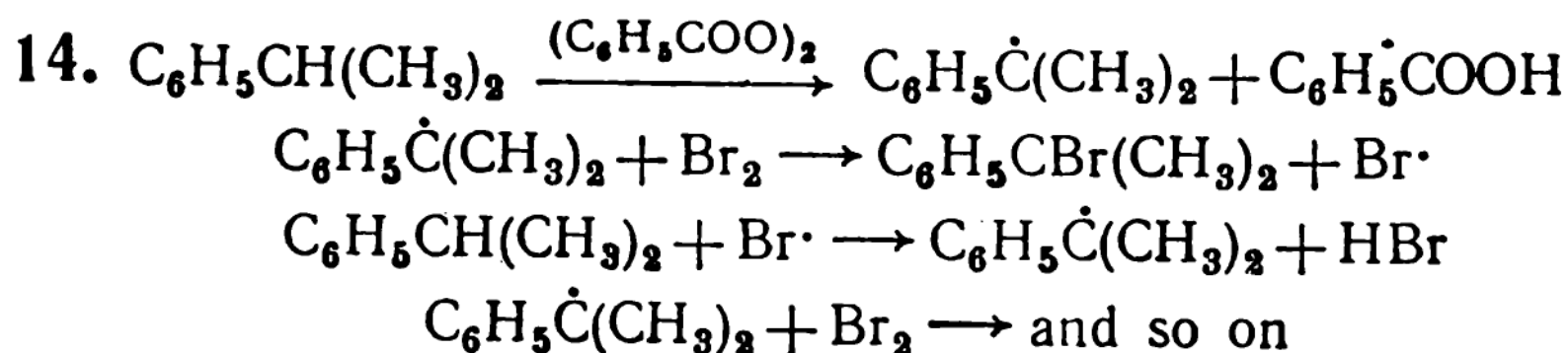
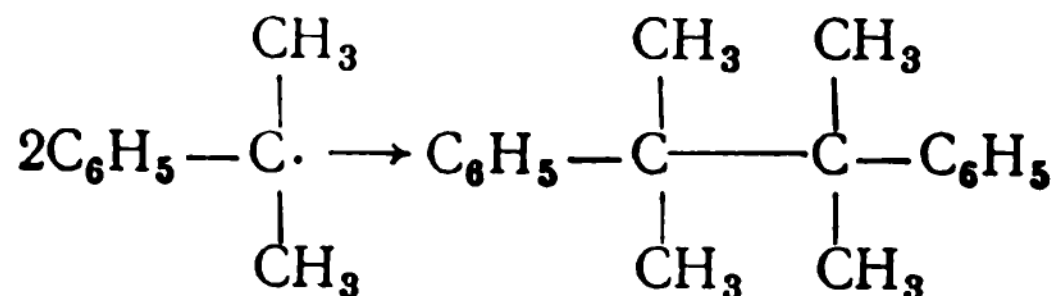
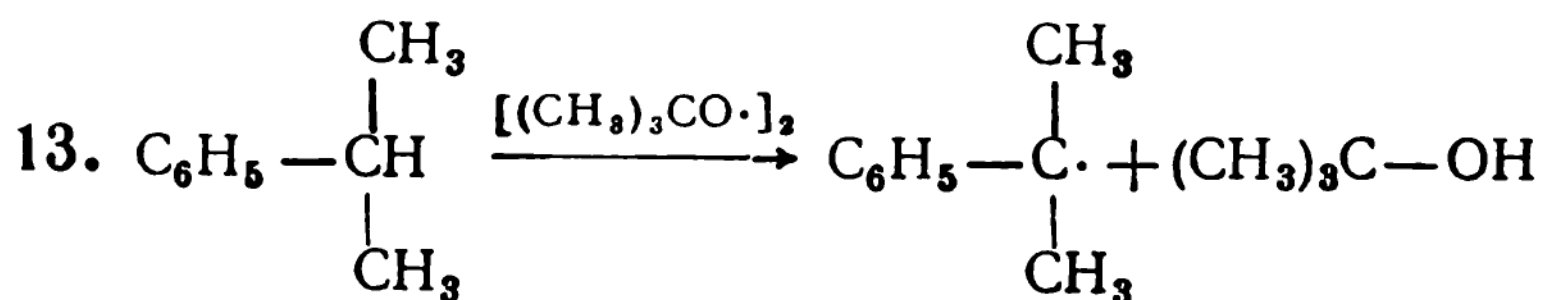


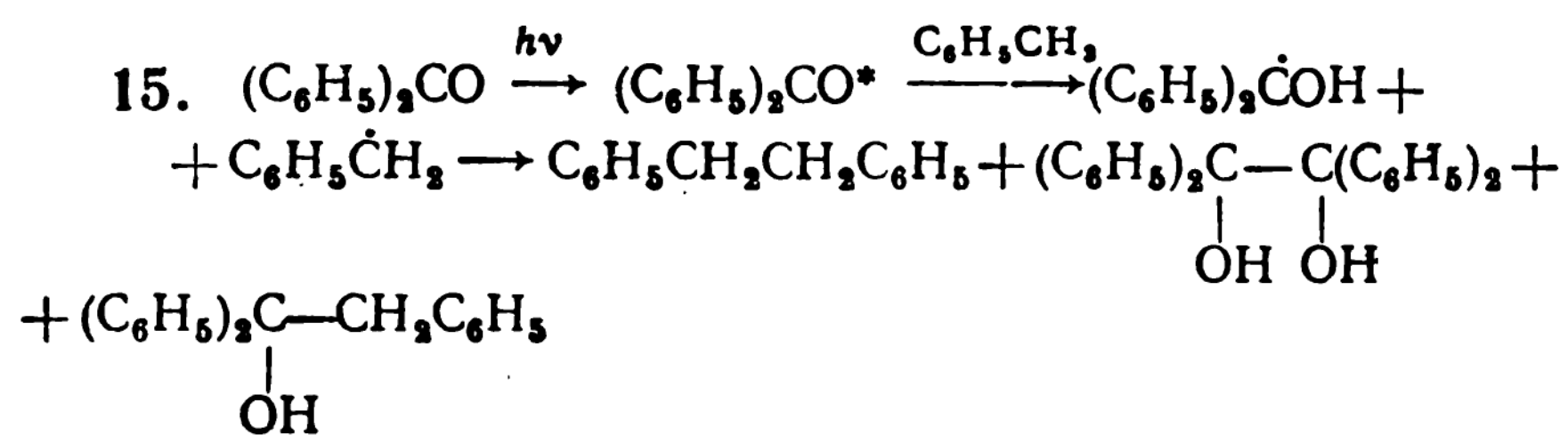
9. The reaction should best be carried out as a photochemical bromination at a low temperature, since this affords a higher selectivity.

10. Both reactions are free-radical processes which proceed through the splitting off of the hydrogen atom and subsequent dimerization of the radical.

11. Apart from the addition, a photochemical substitution reaction may also occur in the light.

12. The observed phenomena are associated with the dissociation of tetraphenylhydrazine, which results in the formation of a free radical—diphenyl nitrogen, $(\text{C}_6\text{H}_5)_2\text{N}^\cdot$. In the presence of hexaphenylethane, which dissociates to form triphenylmethyl, $(\text{C}_6\text{H}_5)_3\text{C}^\cdot$, there is formed a mixed dimer, $(\text{C}_6\text{H}_5)_3\text{C}-\text{N}(\text{C}_6\text{H}_5)_2$, the product of the interaction of two different radicals.



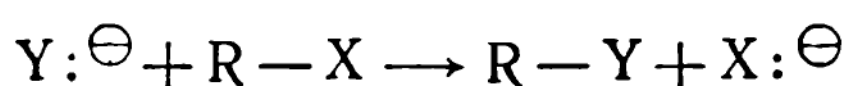


CHAPTER 3

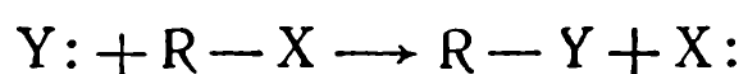
NUCLEOPHILIC SUBSTITUTION IN THE ALIPHATIC SERIES

INTRODUCTION

The important reactions of saturated compounds of the aliphatic series are nucleophilic substitution reactions. General equations for these reactions may be written as follows:



or



The reagent $Y:$ (an anion or neutral molecule) has atoms with unshared pairs of p -electrons and is called a *nucleophile*.

In the reacting molecule $R-X$ (often called a *substrate*) there is a deficiency of electron density at the carbon atom linked directly to the substituent X to be displaced, which is called a *leaving group*.

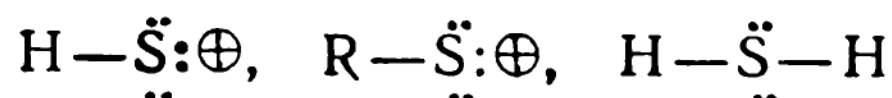
A new covalent bond $C-Y$ in the reaction product is formed due to the unshared electron pair in the nucleophilic reagent $Y:$, and the $C-X$ bond undergoes heterolytic cleavage, the electron pair of this bond being transferred to the group X .

The nucleophilic reagents $Y:$ must have at least one atom with unshared pairs of electrons.

Oxygen-containing nucleophiles include alkali ($H-\ddot{O}:\oplus$), alkoxides of alkali metals ($R-\ddot{O}:\oplus$), anions of carboxylic

acids ($R-\overset{\overset{O}{\parallel}}{C}-\ddot{O}:\oplus$) and water ($H-\ddot{O}-H$).

Sulphur-containing nucleophilic reagents are of an analogous structure:



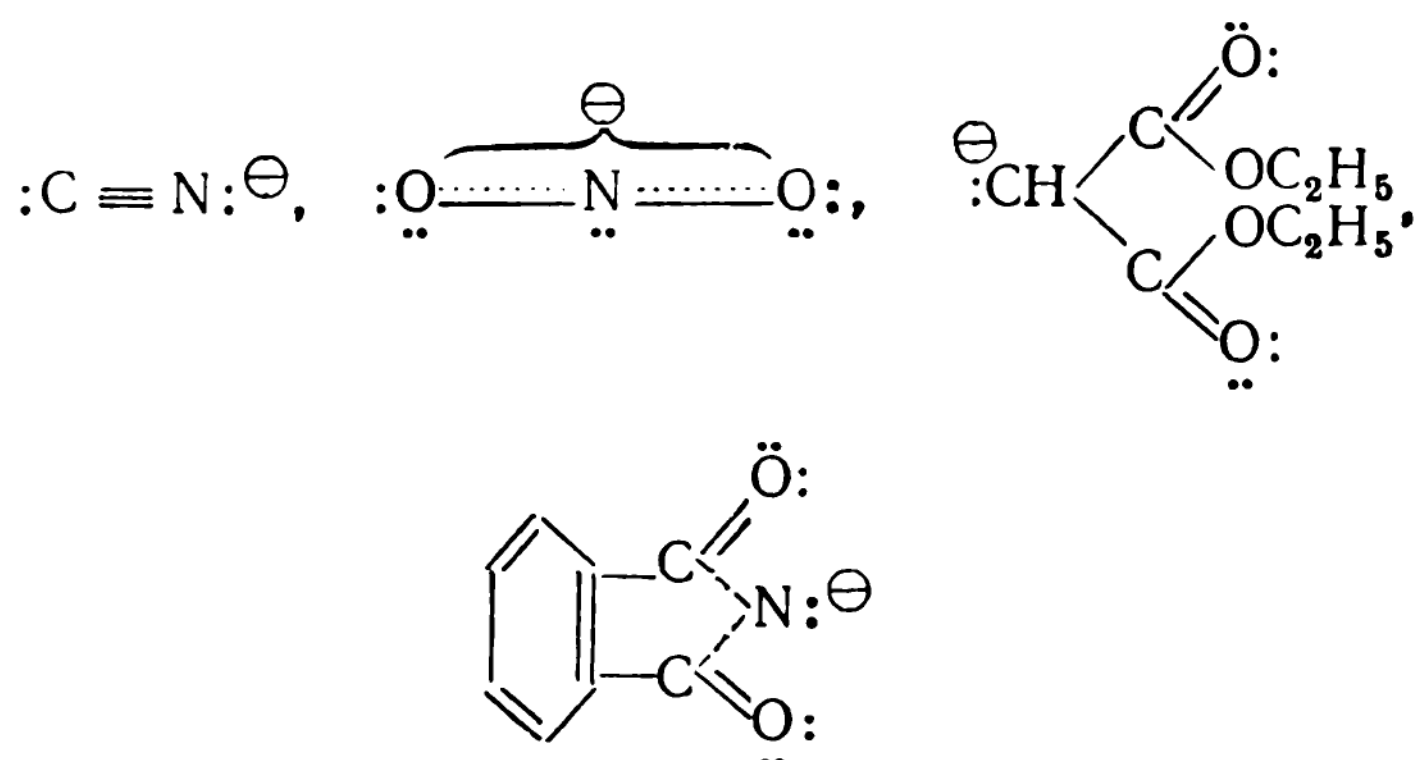
Examples of nitrogen-containing nucleophiles are metal amides ($\text{H}-\ddot{\text{N}}^{\oplus}-\text{H}$) and azides ($:\ddot{\text{N}}^{\oplus}=\ddot{\text{N}}^{\oplus}=\ddot{\text{N}}^{\oplus}:$), ammonia ($\text{H}-\ddot{\text{N}}-\text{H}$), and amines ($\text{R}-\ddot{\text{N}}-\text{R}$).

The halide anions $:\ddot{\text{F}}:\ominus$, $:\ddot{\text{Cl}}:\ominus$, $:\ddot{\text{Br}}:\ominus$, and $:\ddot{\text{I}}:\ominus$ are also nucleophilic reagents.

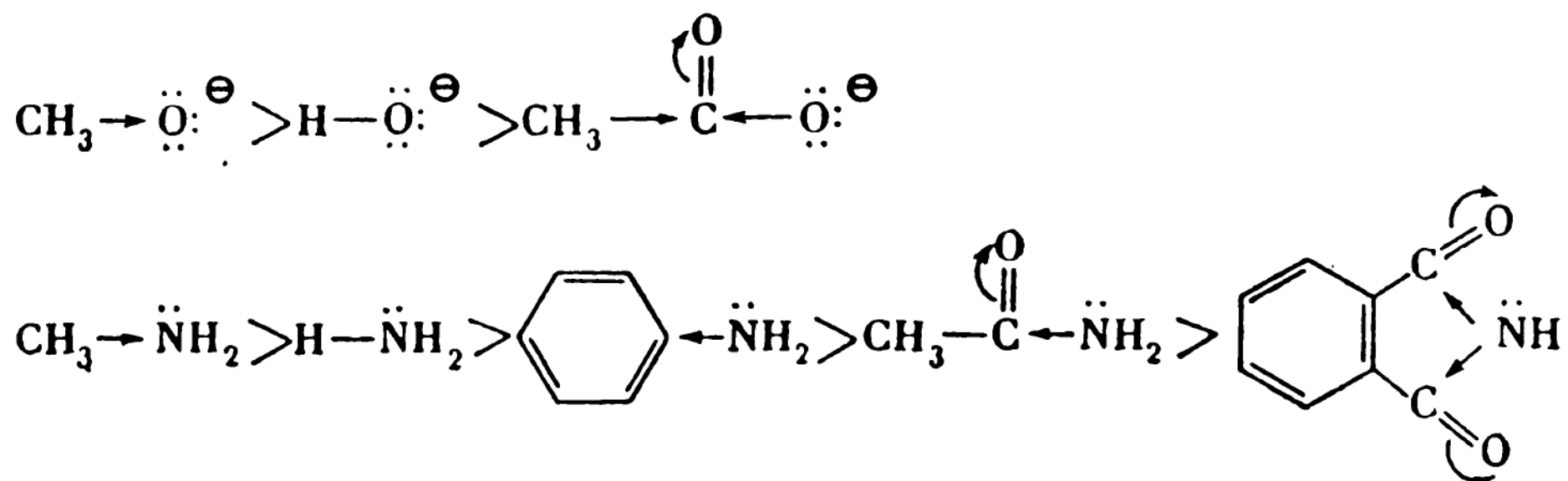
And, finally, carbanions in which the unshared electron pair resides at a carbon atom can also function as nucleophiles. Examples are metal acetylenides ($\text{H}-\text{C}\equiv\text{C}:\ominus$, $\text{R}-\text{C}\equiv\text{C}:\ominus$).

Compounds that contain trivalent phosphorus are more seldom used as nucleophilic reagents.

A nucleophilic reagent may simultaneously contain several different atoms with unshared electron pairs, for example,



The nucleophilic reactivities of elements differ and depend on the position of an element in the Periodic System. The more rightward is the element within a single period the greater is its nuclear charge and the less reactive will be its unshared pairs of *p*-electrons on the outer shell. The nucleophilic reactivity of the elements of any one group of the Periodic System increases with increasing molecular weight. The nucleophilic strength of an atom is strongly affected by the nature of atoms and groups linked directly to it by a covalent bond. Electron-donating groups enhance the nucleophilic strength, whereas electron-accepting ones decrease it. For instance,



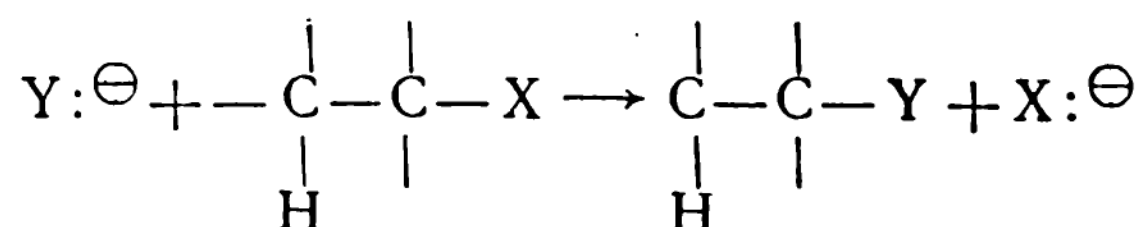
The volume and number of substituents have also a certain effect on nucleophilic reactivity. For example, the reactivity of tertiary amines is somewhat lower than that of primary and secondary amines because substituents create steric hindrances, thereby shielding the unshared electron pair which determines the nucleophilic properties of the nitrogen atom.

The substrates usually taking part in nucleophilic substitution reactions are alkyl halides $\text{R}-\text{Hal}$ in which the halogen atom can be replaced by a large variety of nucleophilic reagents.

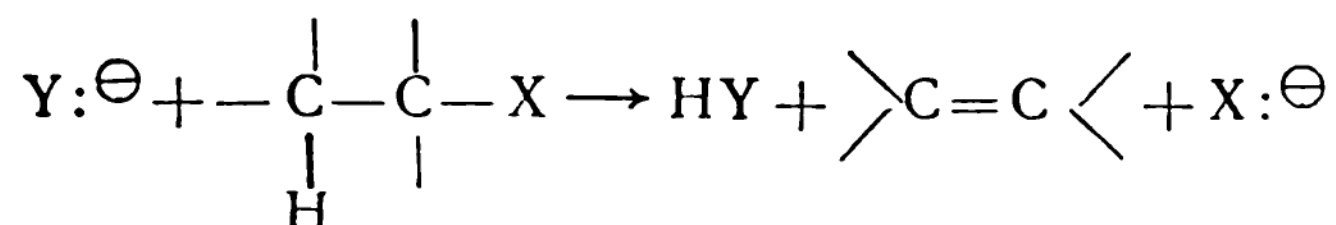
The nucleophilic displacement of the group $-\text{OH}$ in alcohols is more difficult to accomplish. For this reaction to be effected either it must be carried out in an acidic medium or the hydrogen atom of the hydroxyl group must be preliminarily replaced by some electron-accepting group (for example, $-\text{PHal}_2$, $-\text{PHal}_4$, $-\text{SO}_3\text{H}$, or $-\text{SO}_2-\langle \text{=}\rangle-\text{CH}_3$).

Depending on a number of factors, the displacement of a group X in the substrate by a nucleophilic reagent $\text{Y}:^\ominus$ can be accomplished either by the $\text{S}_{\text{N}}1$ or the $\text{S}_{\text{N}}2$ mechanism or else, which is what actually occurs in most cases, by the two mechanisms simultaneously with one of them predominating.

In the overwhelming majority of cases the nucleophilic substitution reactions



are opposed by an elimination reaction involving the formation of an olefin

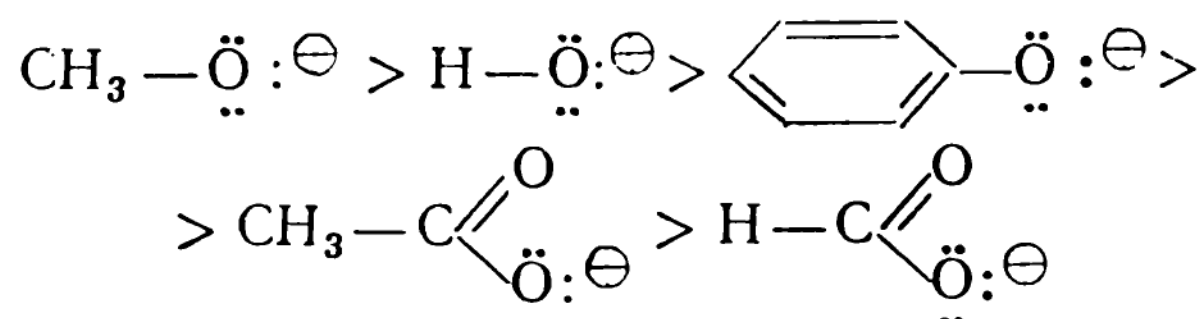


which occasionally exerts a considerable effect on the yield of the product of the nucleophilic substitution reaction.

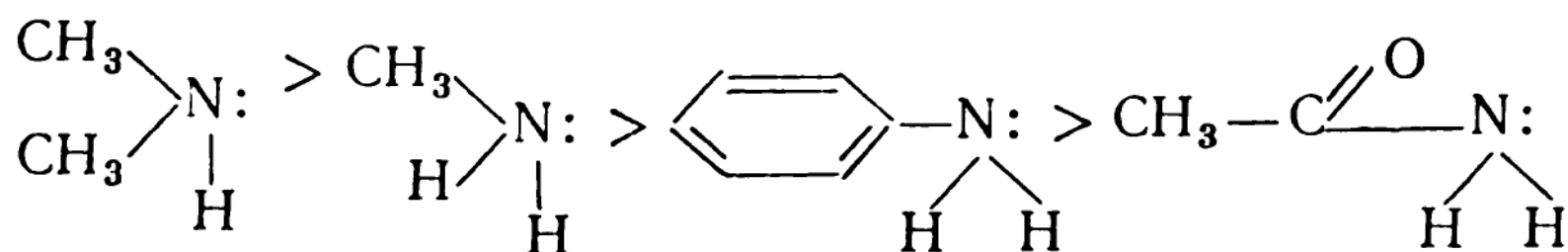
Every nucleophilic reagent is in a larger or lesser degree a base. This means that every nucleophilic reagent capable of donating its unshared electron pair to a carbon atom having a deficiency of electron density is also capable of drawing a proton from compounds with active hydrogen atoms to form, due to this unshared electron pair, a substance which is less dissociated than the original substrate.

The parallelism between nucleophilic reactivity and basicity is not always observed.

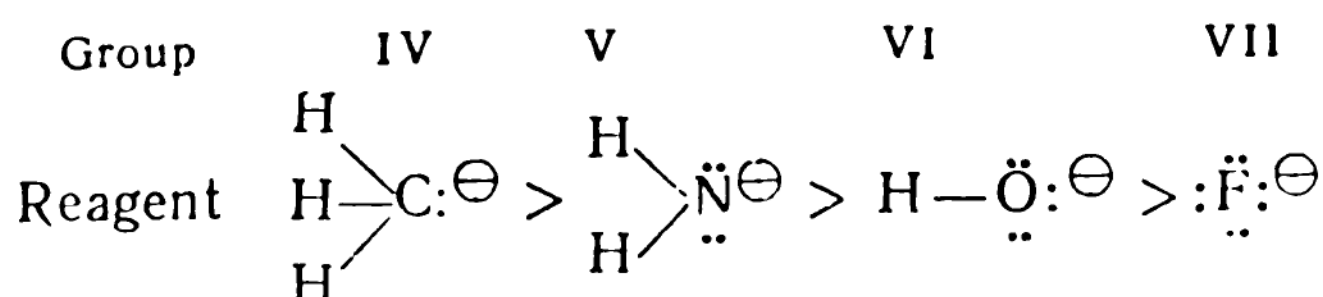
The nucleophilic reactivity and basicity of nucleophiles having the same atom with an unshared electron pair change in parallel; in this case the order of nucleophilic reactivity and basicity is the same:



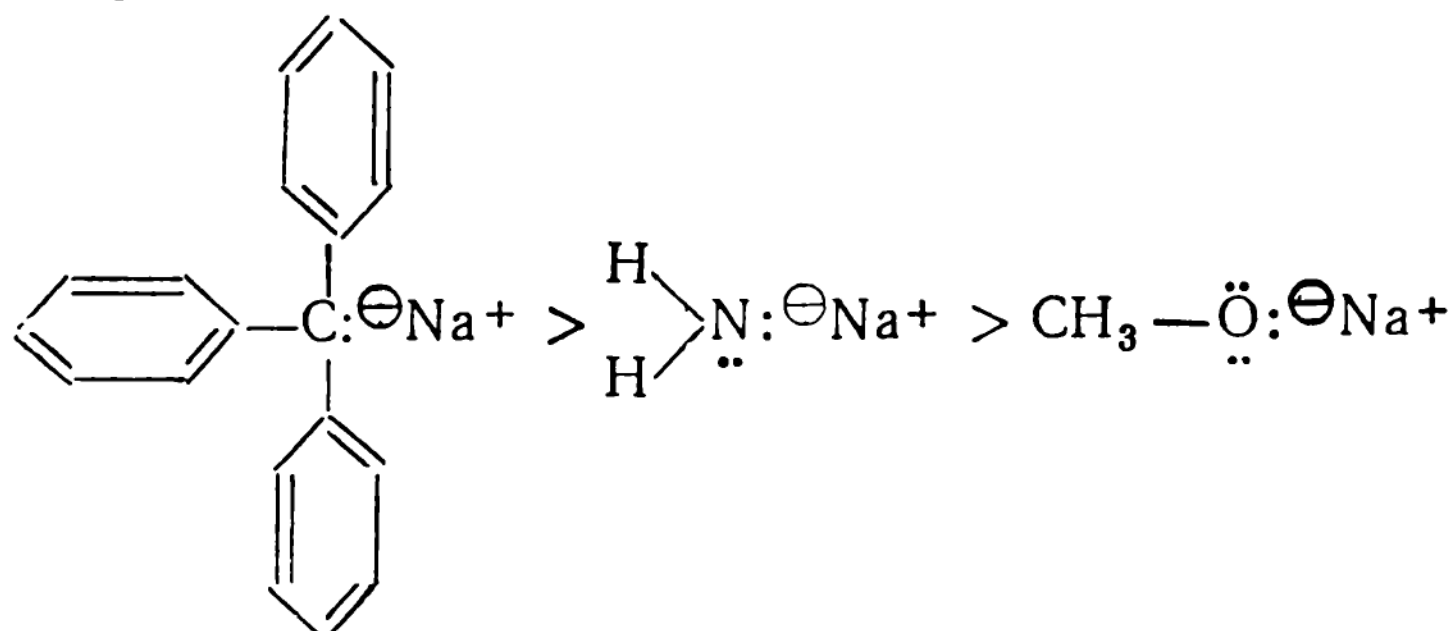
and



The parallelism between nucleophilic reactivity and basicity is also observed when comparing reagents in which the unshared electron pair determining the properties in question is at elements within the same period of the Mendeleyev Table but belonging to different groups:

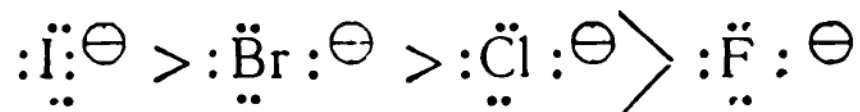


For example, in the series

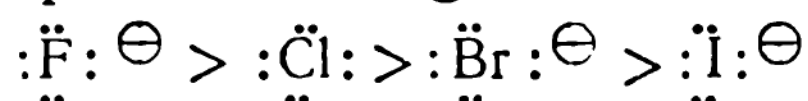


triphenylmethyl sodium is the strongest nucleophile and the strongest base.

But in comparing the nucleophilic activity and basicity of halide anions one can see that the situation is changed; in this case the nucleophilic reactivity decreases in the following sequence



and the basic properties change in the opposite direction



The elimination reactions proceeding concurrently with nucleophilic substitution reactions and observed in those cases when the nucleophile Y^- reacts as a base may follow, depending on a number of factors, two routes designated for convenience as E2 and E1.

For more detailed information on the reactions of nucleophilic substitution at the saturated carbon atom the student is referred to the following books: O. Reutov, *Theoretical Principles of Organic Chemistry*, Mir Publishers, Moscow, 1967; W. H. Saunders, *Ionic Aliphatic Reactions*, Prentice-Hall, Englewood Cliffs, N. Y., 1965.

Problems and Exercises

1. STRENGTH OF ACIDS AND BASES. NUCLEOPHILICITY

1. What is the similarity and the difference between the Brönsted-Lowry and Lewis definitions of acids and bases?

2. Name the conjugate acids of the following bases:
 $\text{C}_6\text{H}_5\text{CH}_2^+$, CH_3OH , $(\text{CH}_3)_2\text{NH}$, $(\text{C}_2\text{H}_5)_2\text{O}$, $(\text{CH}_3)_2\text{N}^+$,

CH_3COOH , H_2O , $\text{CH}_3\text{COO}^\oplus$, $\text{HO}^\oplus$, $\text{CH}_3\text{O}^\oplus$, CH_3CN , CH_3COCH_3 .

3. Name the conjugate bases of the following acids: H_2O , CH_3NH_2 , CH_3NO_2 , $\text{CH}_2(\text{C}_6\text{H}_5)_2$, CH_3CN , $\text{C}_6\text{H}_5\text{NH}_3^+$, $\text{C}_2\text{H}_5\text{OH}$, H_3O^+ , $(\text{NH}_2)_3\text{C}^+$, $\text{CH}_3-\text{C} \begin{smallmatrix} \nearrow \text{OH} \\ \searrow \text{NH}_2^+ \end{smallmatrix}$.

4. What is the effect of the structure of an acid and of its conjugate base on the acidity (basicity) of a compound?

5. Why is guanidine a strong base?

6. Why is aniline a weaker base than cyclohexylamine?

7. Why are BF_3 , ZnCl_2 , AlCl_3 , SnCl_4 and FeCl_3 classed as Lewis acids?

8. How would you calculate the pK_a of CH_3NH_3^+ in water if the K_b of CH_3NH_2 in water is 4.3×10^{-4} ?

9. What is the effect of a solvent on the acidic and basic properties of a substance?

10. How does the strength of acetic acid change in the following solvents: water, benzene, diethylamine?

11. What is the difference in basicity between potassium methoxide and potassium *tert*-butylate? In which of the following media will these compounds exhibit a maximum basicity: the corresponding alcohol, dimethylsulphoxide or hexamethylphosphotriamide (hexametapole)?

12. What are the existing methods for assessing the inductive effect?

13. How is the mesomeric effect evaluated?

14. The dissociation constants of benzoic, *p*-methoxybenzoic and *m*-methoxybenzoic acids are, respectively, 6.27×10^{-5} , 3.38×10^{-5} , and 8.17×10^{-5} . Account for this change of acidity on the basis of known electronic effects.

15. It is known that the strength of halogen-substituted acetic acids XCH_2COOH increases in the sequence $\text{X} = \text{I} < \text{Br} < \text{Cl} < \text{F}$, and in the case of *p*-halobenzoic acids $\text{X}-\text{C}_6\text{H}_4-\text{COOH}$ the reverse order of changing acidity is observed. Explain these facts.

16. Why is *p*-nitrobenzoic acid stronger than *m*-nitrobenzoic acid despite the fact that the nitro group in the *p*-substituted acid is more remote from the carboxyl group?

17. By gradual neutralization of a sulphuric acid solution of a mixture of dimethylaniline and *p*- and *m*-nitrodimethylanilines it is possible to separate these compounds. Predict the sequence of the isolation of the amines during the neutralization.

18. Arrange the following substituted anilines in order of decreasing basicity: *p*-CH₃C₆H₄NH₂, *p*-ClC₆H₄NH₂, *p*-CH₃OC₆H₄NH₂, *m*-O₂NC₆H₄NH₂, *p*-O₂NC₆H₄NH₂, *m*-BrC₆H₄NH₂, *p*-BrC₆H₄NH₂.

19. Arrange the following compounds in order of increasing acidity:

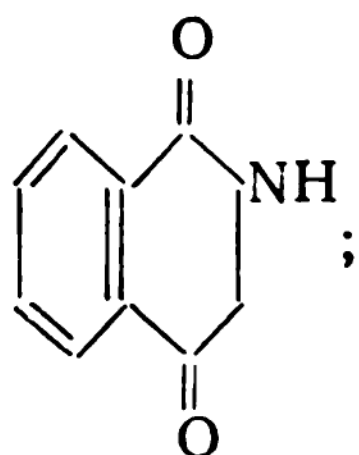
(a) XCH₂COOH, where X = CH₃, F, Br, Cl, I, CH₃O, HOCH₂;

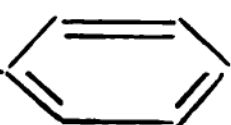
(b) phenol, ethylene glycol, glycerol, isopropyl alcohol, *p*-nitrophenol, *p*-methoxybenzoic acid;

(c) *tert*-amyl alcohol, oxalic acid, acetic acid, formic acid, isobutyl alcohol, *sec*-butyl alcohol, benzyl alcohol;

(d) ethyl alcohol (ethanol), adipic acid, malonic acid, oxalic acid, acetic acid, *tert*-butyl alcohol;

(e) CH₃—CH₂—CH=CH—COOH; CH₃—CH=CH—CH₂—COOH; CF₃—CH=CH—CH₂—COOH; CH₃CH₂CH₂CH₂COOH;

(f) CH₃CONH₂; (CH₃SO₂)₂NH; (CH₃)₃C—C(=O)NH₂; 

(g) X——COOH, where X = NO₂, OH, OCH₃, F, Cl, Br, I, CH₃;

(h) ditto, for the *m*-series.

20. Why does the nucleophilicity series of reagents not always coincide with the basicity (i.e., proton affinity, the tendency to form a bond with a proton) series? Give examples of compounds for which nucleophilicity will differ from basicity.

21. Arrange the following compounds in order of increasing basicity and nucleophilic activity:

- (a) CH_3Na ; CH_3NH_2 ; $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$; $\text{C}_6\text{H}_5\text{OH}$; H_2O ; CH_3ONa ; $\text{C}_6\text{H}_5\text{NH}_2$;
(b) $\text{C}_6\text{H}_5\text{ONa}$; $\text{C}_6\text{H}_5\text{SNa}$; $\text{BrCH}_2\text{COONa}$; CH_3COONa ; $\text{C}_6\text{H}_5\text{NH}_2$;
(c) CCl_3COONa ; $(\text{CH}_3)_3\text{CNa}$; $\text{C}_6\text{H}_5\text{CH}_2\text{ONa}$; $(\text{C}_2\text{H}_5)_3\text{N}$; $\text{C}_6\text{H}_5\text{ONa}$;
(d) $(\text{CH}_3)_3\text{CONa}$; $\text{C}_2\text{H}_5\text{NHNa}$; $(\text{C}_2\text{H}_5)_2\text{NH}$;
(e) $\text{X} - \text{C}_6\text{H}_4 - \text{ONa}$, where $\text{X} = \text{NO}_2, \text{COOCH}_3, \text{CH}_3\text{O}, \text{CH}_3, \text{Br}$.

2. REACTION MECHANISMS, SELECTION OF OPTIMAL REACTION CONDITIONS, REACTIVITY

22*¹. In what order does the mobility of bromine change in the following compounds: 1-bromo-3-methylbutane, 3-bromo-2-methylpent-2-ene, 4-bromo-2-methylbut-2-ene?

23. Suggest a reason for the stability of the following compounds to the action of aqueous alkali: chlorobenzene, vinyl chloride, and neopentyl chloride.

24. Arrange the following alkyl halides in order of decreasing reactivity in a reaction with aqueous alkali: 1-bromobutane, 1-bromobut-1-ene, 4-bromobut-1-ene, 1-bromobut-2-ene.

25*. Compare the reactivities of cyclohexylchloromethane and benzyl chloride in nucleophilic substitution reactions under different conditions.

26. Write structural formulas for the following compounds and arrange them in order of increasing halogen mobility: 4-chloro-2-methylbutane, 6-bromo-2,2-dimethylhexane, 2-bromobut-2-ene, 6-iodo-2-methylhex-2-ene, α -bromoethylbenzene.

27*. In what order does the ease of hydrolysis of primary chloro-, bromo-, and iodoisopentanes change?

28*. Arrange all the isomeric chlorobutanes in order of increasing reactivity in $\text{S}_{\text{N}}2$ reactions.

29*. Diphenylbromomethane, 2-bromo-2-phenylpropane, 2-bromo-2-methylpropane and triphenylbromomethane are heated in aqueous formic acid. Arrange the indicated bromides in order of increasing rate of halogen displacement. What compounds are formed under these conditions?

30. Arrange the following isomeric chlorophenylpropanes in order of increasing reactivity in $\text{S}_{\text{N}}1$ -type reactions: 1-

¹ Problems that are supplied with answers are marked with an asterisk.

chloro-3-phenylpropane, 2-chloro-2-phenylpropane, and 1-chloro-1-phenylpropane.

31*. The bromides A, B, and C have the general formula C_4H_7Br . The treatment of these compounds with lithium (magnesium) in tetrahydrofuran, subsequent hydrolysis and hydrogenation result in the formation of *n*-butane. The compounds A and B do not immediately react with an alcoholic solution of silver nitrate, whereas in the case of C the precipitation of silver bromide begins as soon as the reagent is added. The halide A is relatively inert with respect to an alcoholic solution of potassium hydroxide, the halide B reacts with it on heating, and C reacts in the cold. Suggest possible structures for the compounds A, B, and C.

32*. Arrange the following solvents in order of increasing ability to solvate carbonium ions¹: hexane, dimethylsulphoxide, chloroform, acetone, diethyl ether.

33. Arrange the following compounds in order of decreasing rate of alkali hydrolysis: isopropyl chloride, propyl chloride, *tert*-amyl chloride, 1-chloroprop-1-ene, 3-chloroprop-1-ene.

34. What compounds can be produced by the action of an aqueous solution of potassium hydroxide on 3-chlorobut-1-ene and 4-chloro-2,4-dimethylpent-2-ene? What is the mechanism of these reactions?

35. The ratio of the reaction rates in the hydrolysis of methyl bromide, ethyl bromide, and isopropyl bromide was found to be 2140 : 170 : 5. For what reaction conditions could these data be obtained?

36. The relative rate of the reaction $RBr + H_2O \xrightarrow{HCOOH} ROH + HBr$ for different R is equal to: $CH_3 = 1.00$, $C_2H_5 = 1.71$, *iso*- $C_3H_7 = 44.7$, *tert*- $C_4H_9 = 10^8$. What is the mechanism of this reaction? Does the rate of this reaction depend on the concentration of water?

37. The ratio of the rates of hydrolysis of isopropyl bromide (in 80 per cent ethanol, at 55°C) by the uni- and bimolecular mechanism is 21. How can this ratio be reduced and increased?

38*. Under what conditions should ethyl bromide and 2-bromo-2-methylpropane be hydrolysed to give a maximum yield of the alcohols?

¹ An organic anion is called a *carbanion*; an organic cation is known as a *carbonium ion*.—*Tr.*

39. Under what conditions will *tert*-butyl chloride be hydrolysed and ethyl γ -chlorobutyrate remain practically unchanged?

40*. What compounds can be produced by hydrolysis of crotyl chloride with (a) an aqueous solution of potassium hydroxide, and (b) a water-acetone mixture?

41. Under what conditions can crotyl alcohol be prepared from crotyl chloride with no but-1-en-3-ol present?

42*. Arrange the following solvents in order of increasing rate of hydrolysis of *tert*-butyl in them: water, aqueous acetone, aqueous formic acid, moist benzene, aqueous alcohol.

43. In what order will the reactivity of the halogen change in the following bromopentanes: *n*-amyl bromide, 1-bromo-2,2-dimethylpropane, and 2-bromopentane if the reaction is carried out with the use of a suspension of dry sodium ethoxide in pentane?

44*. The relative rates of the formation of ethers from sodium ethoxide and ethyl, propyl, isopropyl and neopentyl bromides are equal to 100, 28, 3, and 4×10^{-4} , respectively. How would you account for these results?

45. The rate ratio of the reaction of sodium alkoxide in nonaqueous ethyl alcohol (ethanol) at 55°C with methyl, ethyl, propyl, butyl, and amyl bromides is 17.6 : 1 : 0.3 : 0.23 : 0.21. How can this fact be accounted for?

46*. Suggest a method for preparing ethyl-*tert*-butyl ether.

47. Suggest starting materials and optimal conditions for preparing butyl ethyl ether by the Williamson reaction.

48. In which of the following solvents will it be expedient to prepare benzyl phenyl ether by the Williamson reaction: water, dioxane, benzyl alcohol, hexane?

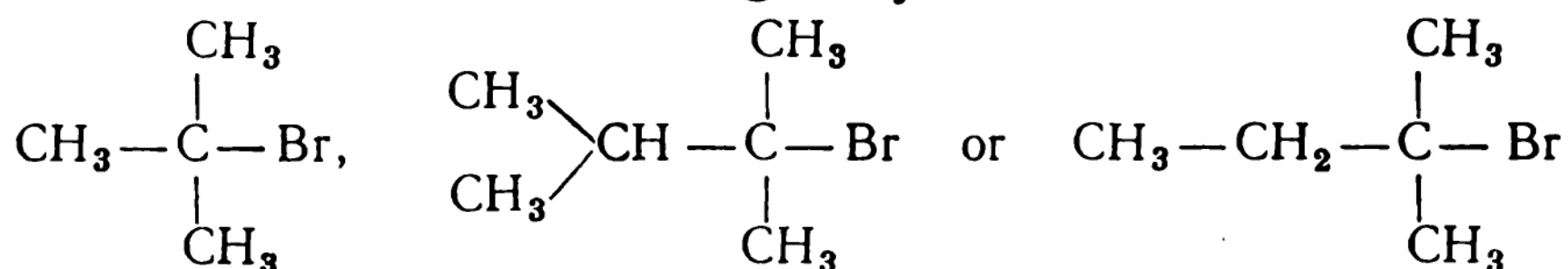
49. Suggest the most efficient method for synthesis of *tert*-butyl methyl ether.

50. Outline the possible ways of preparing the ethers ArOCH_2R and $\text{ArCH}_2\text{OCH}_2$.

51. In what sequence does the rate of alcoholysis of *n*-propyl iodide, chloride and bromide in acetone change?

52*. How can you explain the fact that under comparable conditions butyl bromide reacts with $\text{C}_4\text{H}_9\text{SNa}$ 1830 times faster than with $\text{C}_4\text{H}_9\text{ONa}$ and that the yield of dibutyl thioether is higher than that of dibutyl ether?

53. Which of the following alkyl halides



in a reaction with sodium alkoxide gives the highest yield of an olefin as a by-product?

54*. What olefin is formed by the action of sodium alkoxide on 4-bromo-2,2,4-trimethylpentane? Explain why.

55. Explain why the yield of the substitution products resulting from the interaction of *sec*-butyl chloride with sodium methoxide, potassium phenolate and sodium iodide in methanol increases in the sequence in which the reagents are enumerated. What are the end products of these reactions?

56. Which of the bromine atoms in 1,3-dibromo-1-(*p*-bromophenyl)-propane will be displaced more readily by a cyano group under the action of sodium cyanide in dioxane?

57. Suggest optimal conditions for the synthesis of nitriles from sodium cyanide and isopropyl bromide, diisopropylbromomethane and *n*-butyl bromide.

58*. Suggest optimal conditions for the conversion of isopropyl bromide into (a) 2-nitropropane and (b) isopropyl nitrite.

59*. Using electronic formulas, explain why the reaction of *n*-butyl bromide with sodium nitrite or potassium cyanide may result, in each case, in the formation of two compounds of different structure.

60. What compounds are predominantly formed in the reaction of *sec*-butyl bromide with potassium cyanide in dimethylsulphoxide and hexane?

61*. What is the predominant route of the reaction of crotyl chloride with potassium cyanide in (a) water; (b) dimethylsulphoxide, and (c) hexane?

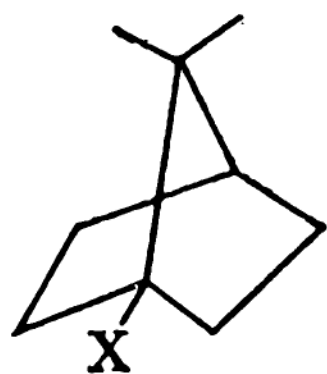
62. The relative rates of the reaction $\text{I}^\oplus + \text{RBr} \xrightarrow{\text{Acetone}} \text{RI} + \text{Br}^\oplus$ for different R are equal to: $\text{CH}_3 = 1.00$; $\text{C}_2\text{H}_5 = 0.065$; *iso*- $\text{C}_3\text{H}_7 = 0.005$; *tert*- $\text{C}_4\text{H}_9 = 0.00039$. What is the mechanism of this reaction? How will the rate of this reaction change with change of the concentration of the nucleophilic reagent?

63. It is known that optically active alkyl iodides, say, secondary butyl iodide (this refers to alkyl bromides as well),

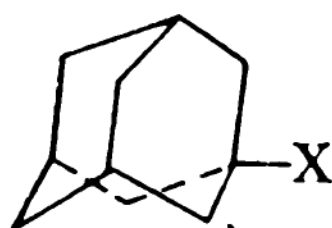
in acetone or some other aprotic dipolar solvent are racemized in the presence of sodium iodide (alkyl bromides are racemized in the presence of sodium bromide). It has also been found that the rate of racemization is proportional to the concentration of sodium iodide (bromide). What conclusions can be made concerning the mechanism of this reaction on the basis of these data?

64. Why does methyl iodide containing radioactive iodine lose its radioactivity in an acetone solution of non-radioactive sodium iodide?

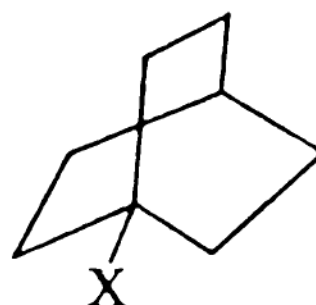
65*. On the basis of the concepts of the S_N1 mechanism, predict the relative reactivity of the following bi- and tri-cyclic systems under conditions most favourable for conversions via the S_N1 route:



(I)

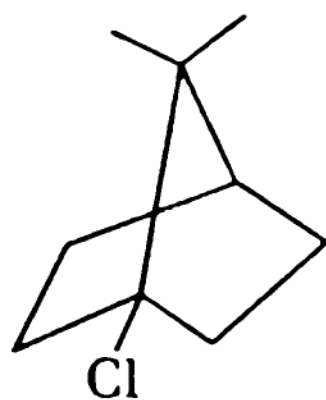


(II)



(III)

66*. It is known that tertiary alkyl halides react very rapidly with an aqueous-alcoholic solution of silver nitrate. An exception is 1-chloroapocamphane (IV)



(IV)

which does not react with the silver nitrate solution even for 48 hours. Explain this result.

67*. It has been found that the intramolecular hydrogen bond in *dl*-butane-2,3-diol is stronger than that in a meso-isomer. This inference has been drawn on the basis of a study of the IR spectra of the specified compounds and confirmed by other data. Explain this phenomenon.

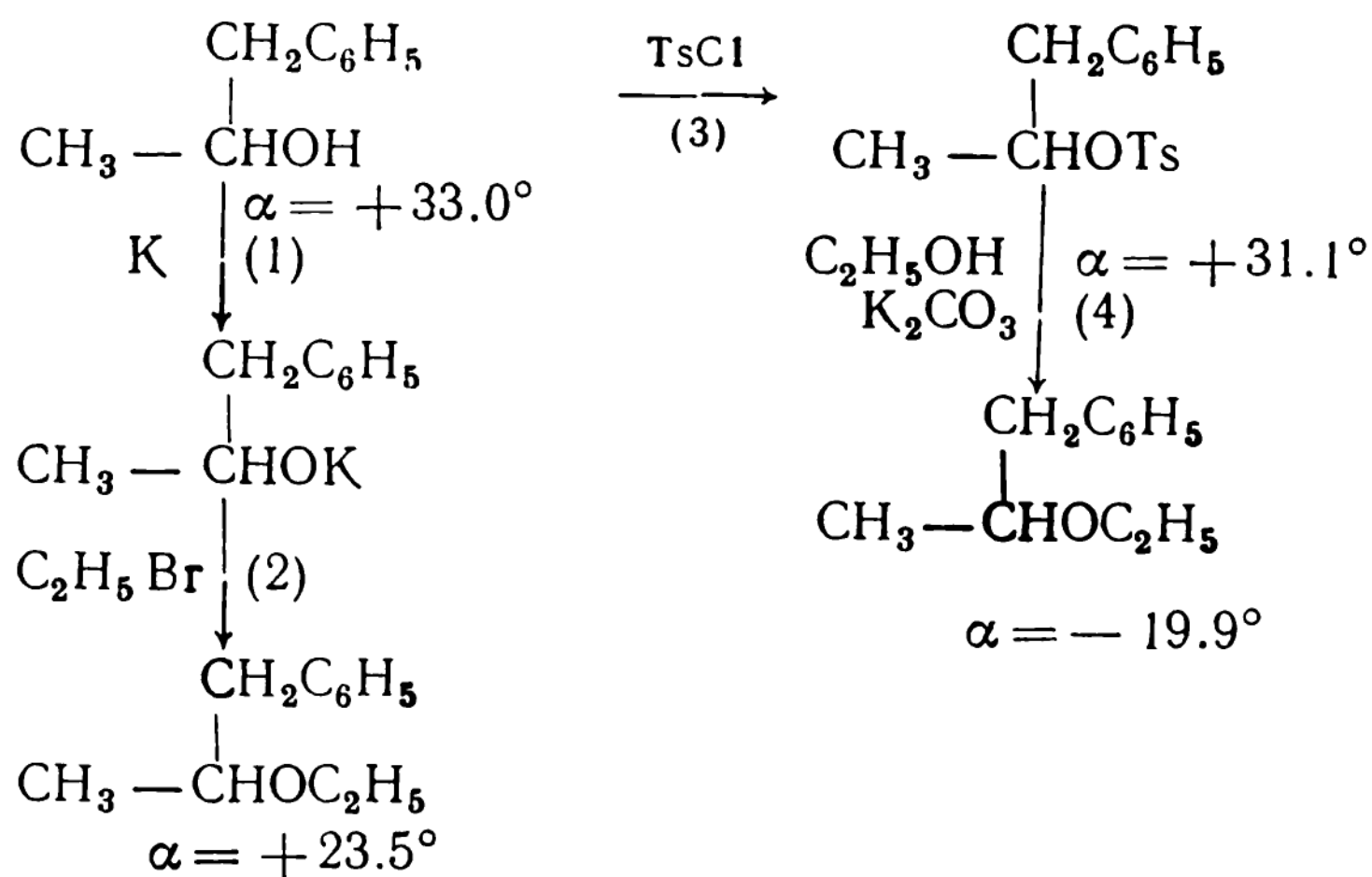
68*. It is known that tertiary butyl alcohol acted on by concentrated hydrochloric acid is readily converted into the corresponding chloride, whereas *n*-butyl alcohol reacts much

slower under the same conditions. Explain why these alcohols behave differently.

69*. The dehydration of methyl-*tert*-butylcarbinol with the aid of strong protic acids yields a mixture of unsaturated hydrocarbons, the main component of which is tetramethylethylene. How can you account for this course of the reaction?

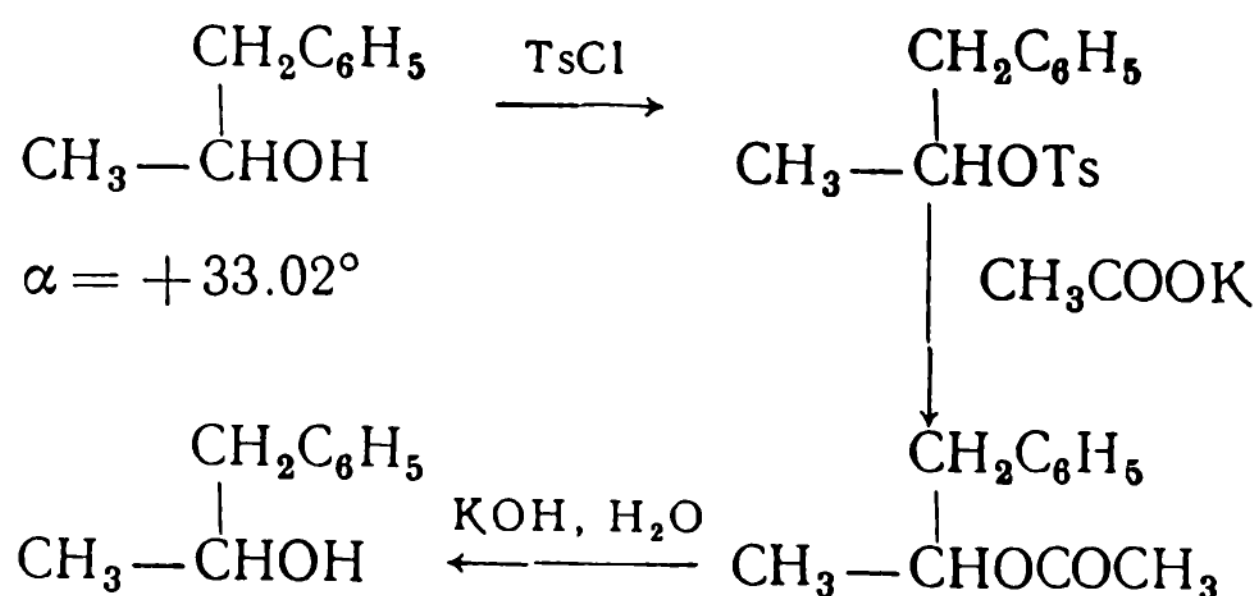
70*. When heated with sulphuric acid, neopentyl alcohol forms an unsaturated hydrocarbon which on ozonization is converted to acetone and acetaldehyde. Suggest a structure for this hydrocarbon and write the scheme of its formation.

71*. Consider the following scheme of conversions of optically active 1-phenylpropan-2-ol. Indicate in which cases the reactions proceed with retention of the configuration of asymmetrical carbon atom and in which its inversion takes place:



TsCl stands for $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$

72*. Predict the stereochemical result of the following conversions:



Can it be expected that the 1-phenylpropan-2-ol resulting from this reaction will be optically active?

73*. The treatment of optically active *erythro*-3-bromobutan-2-ol with concentrated hydrobromic acid leads to the formation of *meso*-2,3-dibromobutane. Under the same conditions optically active *threo*-3-bromobutan-2-ol is converted to *dl*-2,3-dibromobutane. How could you account for these results?

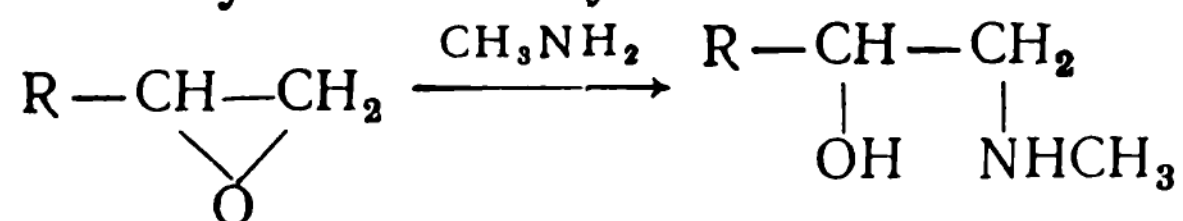
74. Why does the sodium salt of methylsulphuric acid react slower with sodium phenolate in methanol than dimethylsulphate?

75*. Why is hydriodic acid more active than hydrobromic acid in reactions of ether cleavage?

76*. What compounds are formed when hydrogen iodide attacks anisole, ethyl-*tert*-butyl ether, benzyl propyl ether, and methyl isopropyl ether? Formulate the mechanism of these conversions.

77*. Which of the following ethers is more readily split by hydriodic acid: ethyl isopropyl ether, diethyl ether, methyl-*tert*-butyl ether?

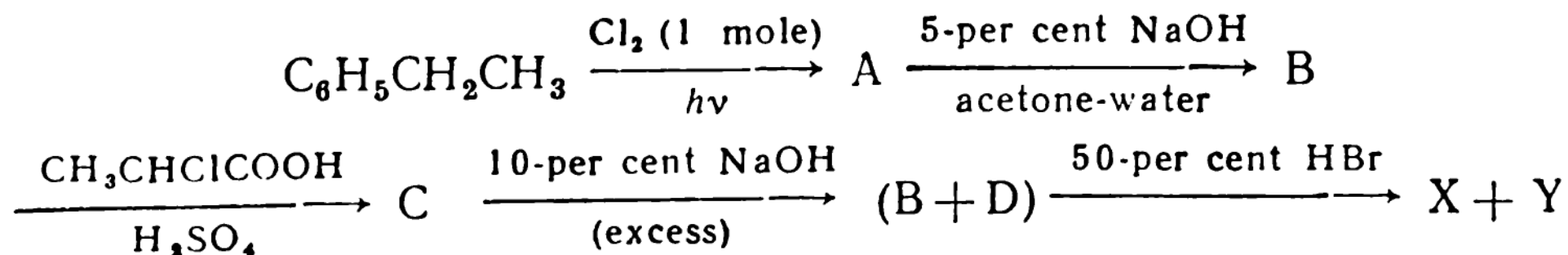
78*. The oxide ring is broken by amines in such a manner that the amino group preferably attacks the primary rather than the secondary or tertiary carbon atom:



What conclusions could be drawn as to the mechanism of this reaction from this fact?

79*. What compound is formed when isobutylene oxide is treated with a solution of dry hydrogen chloride in methanol? Discuss the mechanism of this conversion.

80*. What will result from the following reactions?



Discuss the mechanisms of these reactions.

81*. Which of the following reagents can be used to convert phenylacetic acid to its methyl ester in a maximum yield (without the use of additional reagents): methanol, diazomethane, methyl iodide, dimethyl sulphate?

82*. How could you account for the fact that the rates of esterification of acetic, propionic, isobutyric, and pivalic (trimethylacetic) acids with ethanol decrease in the sequence in which the acids are listed?

83*. Arrange the following alcohols in order of decreasing rate of their esterification with chloroacetic acid: *tert*-amyl, isobutyl, isopropyl, and methyl alcohols? Write the schemes of the corresponding reactions.

84*. Write the equations for the reactions of ketene with isobutyl alcohol, acetic acid, ethylamine and hydrogen chloride, and discuss their mechanism.

85. One of the widely used methods for synthesis of esters consists in treating primary or secondary (but not tertiary) alcohols with carboxylic acid halides. Give your suggestions as to what side reactions are involved in the case of tertiary alcohols.

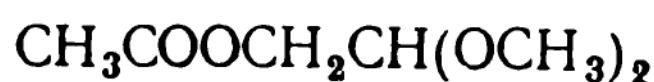
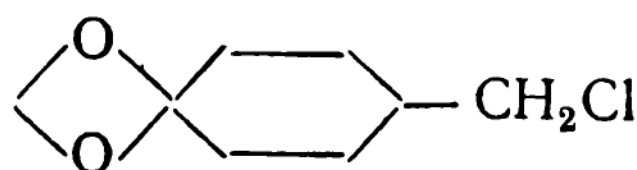
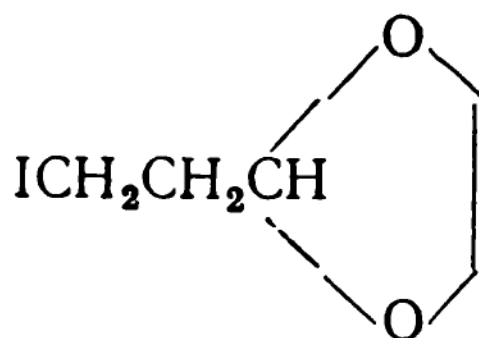
86. To produce *tert*-butyl esters of carboxylic acids, use is often made of the following method: carboxylic acid is added to a solution of isobutylene (taken in a large excess with respect to the acid) in methylene chloride and then 3 to 5 per cent (in terms of carboxylic acid) of concentrated sulphuric acid is added to the mixture. The yields of esters are, as a rule, preparative. Discuss the scheme of the mechanism of the conversions involved.

87. The rates of the acid hydrolysis of the esters $(\text{CH}_3)_3\text{CCH}_2\text{COOC}_2\text{H}_5$ and HCOOC_2H_5 are in the ratio of 1 : 10^5 . What is the cause of this difference?

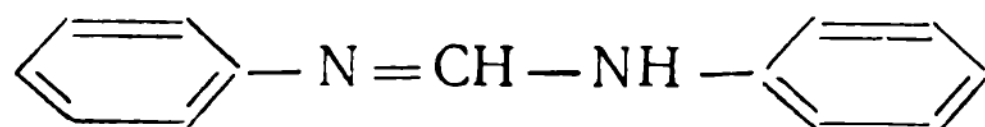
88. The rates of the alkali hydrolysis of ethyl trimethylacetate and ethyl trichloroacetate are in the ratio of 1 : 10^7 . How can you account for this difference?

89. In what sequence does the rate of the alkali hydrolysis of methyl ether, ethylamide, and butyric anhydride change?

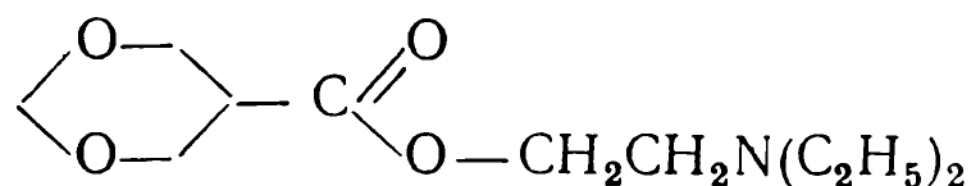
90. Suggest methods for the selective hydrolysis of the halides and derivatives of the functional groups in the following compounds:



91. What compounds result from the complete hydrolysis of a compound of the following structure?



92. Write the scheme of hydrolysis of a compound having the following structure:



3. THE USE OF NUCLEOPHILIC SUBSTITUTION REACTIONS FOR SYNTHETIC PURPOSES

The synthetic importance of reactions of the type considered is great and they are used to produce the various classes of compounds. We will however be concerned only with the simplest cases since this section, like the chapter as a whole, is intended for the beginning student of organic chemistry.

It is necessary that the student should make a preliminary thorough study of the first sections of this chapter and also of Chapter 2. It is only a knowledge of the regularities of the course of nucleophilic substitution reactions that will help choose the proper pathway of synthesis and the optimal conditions for carrying out the various conversions.

First are given problems in nucleophilic displacement of a halogen and of the hydroxyl group and also in the synthesis of ethers and esters (Problems 93-118), and then problems in the introduction of the amino group into a molecule of an organic compound with the aid of nucleophilic substitution reactions (Problems 119-135) and rearrangements (Problems 136-143).

Most of the problems given deal with actual paths of synthesis that find practical application. Some of the problems, in which the simplest organic compounds are used as starting materials, are given to stimulate thought and ingenuity rather than to illustrate the actual paths of synthesis.

Answers are supplied to all the problems.

93. By using available organic solvents and inorganic reagents prepare the following compounds from propylene:

(a) allyl alcohol; (b) *n*-butyric acid; (c) isopropyl iodide; (d) 2-nitropropane; (e) isopropyl nitrite. Write the schemes of the reactions used.

94. Prepare the following compounds from isobutyl alcohol: (a) *tert*-butyl chloride; (b) 3-nitro-2-methylpropene; (c) diisopropenyl sulphide. Give the equations of the corresponding reactions.

95. Synthesize the following compounds from cyclohexanol: (a) cyclohexanecarboxylic acid; (b) cyclohexen-3-ol; (c) cyclohexene-3-carbonitrile. Write the equations of the corresponding reactions.

96. Suggest a path for synthesis of 2-methylbutane-3-thiol from 2-methylbut-2-ene.

97. Prepare methyl cyanoacetate from methyl alcohol without the use of other organic reagents.

98. Prepare the following compounds from ethanol and inorganic reagents: (a) malonic ester; (b) ethyl α -bromopropionate. Write the equations of the reactions involved.

99. Prepare nitromethane by using only inorganic reagents.

100. Using inorganic reagents and *n*-propyl alcohol, synthesize: (a) 1,3-dibromopropane; (b) glycerine; and (c) allyl iodide.

101. Without using organic reagents other than ethyl alcohol, prepare: (a) β -hydroxypropionic acid; (b) ethylene glycol diacetate.

102. Using methyl alcohol and inorganic reagents, synthesize: (a) dimethyl thiodiacetate; (b) thioglycolic acid.

103. Using methyl alcohol and inorganic reagents, prepare: (a) methoxyacetic acid; (b) acetoxyacetic acid; (c) acetic anhydride.

104. Synthesize 2,4-dimethylpentan-3-one from propylene.

105. Name methods for the synthesis of alkyl iodides.

106. There are three most widely used methods for synthesizing unsymmetrical ethers: (a) the heating of a solution of solid potassium hydroxide in the corresponding alcohol with alkyl iodide or bromide; (b) the autoclave heating of a dry alkoxide of the corresponding alcohol with an alkyl halide (usually bromide); (c) the boiling of the corresponding alkoxide in an excess of the same alcohol with an alkyl halide. What ethers can be made by these methods? Which of them enables ethers to be synthesized in maximum yields?

107. Give examples of the synthesis of ethers from alcohols by the action of concentrated sulphuric acid.

108. What is the most general method of preparing primary alkyl fluorides?

109. What compounds will be obtained from 2-methylbutan-3-ol by the action of the following reagents on it: (a) hydrogen chloride on heating and then a suspension of potassium cyanide in ether; (b) metallic sodium and then methyl iodide; (c) propionyl chloride; (d) phosphoric acid on heating?

110. Name ten methods for preparing esters.

111. Prepare isopropyl propionate from propylene and inorganic reagents. Write the equations of the corresponding reactions.

112. Prepare isopropylisobutyrate from isopropyl alcohol and inorganic reagents.

113. Prepare the following compounds from phenol and ethyl alcohol without using other organic reagents: (a) phenetole (ethoxybenzene or phenyl ethyl ether); (b) 1,2-diphenoxyethane; (c) phenoxyacetic acid.

114. Prepare phenylacetic acid and also its ethyl ester and nitrile from toluene and the simplest reagents.

115. Prepare the following compounds from toluene without resorting to oxidation reactions: (a) benzyl alcohol; (b) benzaldehyde; (c) benzoic acid; (d) benzoyl peroxide.

116. Synthesize the following compounds from methyl alcohol (methanol), phenol and inorganic reagents: (a) anisole; (b) methyl phenoxyacetate; (c) mixed anhydride of acetic and phenoxyacetic acids; (d) phenol acetate.

117. It is known that *o*-xylene when subjected to free-radical bromination is converted to tetrabromide (two bromine atoms are incorporated into each methyl group). Suggest a method for preparing *o*-phthalic aldehyde from *o*-xylene.

118. Prepare (a) dibenzyl ketone and (b) benzyl benzoate from toluene and inorganic reagents.

119. Prepare the following compounds by nucleophilic substitution reactions: (a) N, N-diethylallylamine; (b) ethanolamine; (c) triethanolamine.

120. Suggest a method for preparing nitrogen mustard — β , β' , β'' -trichlorotriethylamine—from ethanol and inorganic reagents.

121. How can the antiradiation protective compound β -mercaptoethylamine be synthesized from ethanol?

122. Suggest a reaction path for synthesis of N,N-diethylethylenediamine from ethanol and other available reagents.

123. Suggest a method for preparing Trilon B—N,N,N',N'-ethylenediaminetetraacetic acid—from ethanol.

124. Explain why the Hofmann synthesis of amines from halogen derivatives and ammonia is hardly suitable for making pure diethylamine but gives better results when amines of higher molecular weight, say, di-*n*-hexylamine, are synthesized.

125. How can *n*-propylamine containing no secondary and tertiary amines as impurities be prepared?

126. Using ethanol, aniline, and inorganic reagents, prepare (a) N,N'-diphenylpiperazine; (b) monoethanolaniline.

127. Synthesize 2-diethylamino-1-phenylethan-1-ol from ethylbenzene and ethanol.

128. Synthesize γ -aminobutyric acid from propylene and available reagents.

129. How can (a) 4-aminobutan-1-ol and (b) tetramethylethylenediamine be prepared from tetrahydrofuran?

130. What methods of synthesizing asymmetrical secondary amines do you know?

131. Suggest a method for preparing α -aminobutyric acid from *n*-propyl alcohol and inorganic reagents.

132. Synthesize anilide of thioglycolic acid (an analytical reagent for cobalt) from aniline, acetic acid and inorganic reagents.

133. Suggest a method for synthesizing N-acetylacetamide from acetic acid.

134. How can optically active butan-2-ol be converted to 2-aminobutane with optical activity being retained?

135. Synthesize N-ethyl-N- β -hydroxyethylaniline from aniline, ethyl alcohol and inorganic reagents.

136. Give eight reaction paths for synthesis of *n*-propylamine, involving only nucleophilic substitution and rearrangement reactions.

137. What compounds result in the Hofmann rearrangement from the amides of (a) methylethylacetic acid, and (b) phenylacetic acid?

138. Name the products that can be obtained in the Curtius

rearrangement from the azides of (a) α -methylcrotonic acid and (b) lactic acid.

139. How can succinic acid be converted to β -alanine?

140. The treatment of 1 mole of acetamide with 0.5 mole of potassium hydroxide and bromine results in the formation of N-methyl-N-acetylurea. How can this conversion be accounted for?

141. What compounds are formed from the oximes of cyclopentanone and cyclohexanone by the Beckmann rearrangement?

142. Prepare benzoic acid and aniline from benzophenone and inorganic reagents.

143. Write the schemes of conversions, under the conditions of the Beckmann rearrangement, of the following: (a) stereoisomeric oximes of α -indanone (indone); (b) oximes of 2,4-dimethylcyclohexanone.

Answers

1. The similarity between these definitions is that a base is thought to be a substance possessing an unshared pair of electrons.

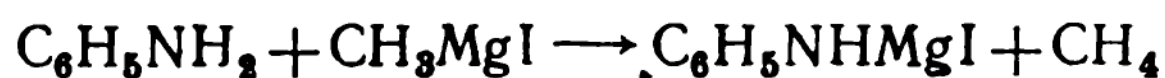
According to Brönsted and Lowry, a substance may be regarded as an acid if it is capable of donating a proton: $\text{acid} \rightleftharpoons \text{H}^+ + \text{base}$. In such a case the base is known as the conjugate base of the acid and the acid, as the conjugate acid of the base. Thus, acids are proton-donors and bases, proton-acceptors.

Lewis defined acids as substances or particles deficient in electrons (e.g., H^+ , BF_3 , AlCl_3), i.e., as substances or particles with their outer electron shell being incomplete. This definition of acids is more general than the Brönsted-Lowry definition.

Most of proton-containing substances have heteroatoms with an unshared pair of electrons and one may speak therefore of the acidic or basic properties of compounds only with respect to any other substance when these properties are displayed in a concrete reaction—an acid-base equilibrium.

For example, water and aniline in the reaction $\text{C}_6\text{H}_5\text{NH}_3^+ + \text{H}_2\text{O} \rightleftharpoons \text{C}_6\text{H}_5\text{NH}_2 + \text{H}_3\text{O}^+$ are bases (and the anilinium and

hydroxonium cations are acids); the water in the reaction $\text{C}_2\text{H}_5\overset{\oplus}{\text{O}} + \text{H}_2\text{O} \rightleftharpoons \text{C}_2\text{H}_5\text{OH} + \text{H}\overset{\oplus}{\text{O}}$ is an acid just like aniline in the reaction



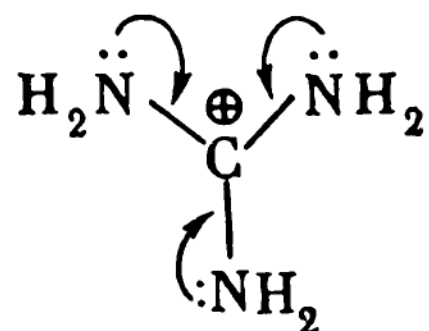
The dissociation of protic acids is an equilibrium process which consists in the distribution of a proton between two bases: the conjugate base of an acid and the solvent. For instance, in the dissociation of acetic acid in water ($\text{CH}_3\text{COOH} + \text{H}_2\text{O} \rightleftharpoons \text{CH}_3\text{COO}^- + \text{H}_3\text{O}^+$) the protons are distributed between the acetate ion and the water. The degree of dissociation (i.e., the strength of an acid) therefore greatly depends on the solvent (see answer to Problem 9).

The concept of acidity and basicity is one of the most general conceptions in chemistry¹, and to understand the essence of organic heterolytic reactions (especially, those associated with proton-transfer) it is always necessary to consider acid-base equilibria in a system and the causes of their shifting. This is especially important in studying reversible reactions catalyzed by acids and bases, for example, acylation, ester condensation, diazotization, Friedel-Crafts alkylation.

2-3. Use should be made of the definition given in the previous answer.

4. The weaker (more stable) the base, the stronger its conjugate acid and vice versa. The stability of a base (with a charge on the same heteroatoms) is the higher, the more delocalized is the charge due to the mesomeric or inductive effect. For example, $\text{CF}_3\text{COO}^\oplus$ is much weaker as a base than $\text{CH}_3\text{COO}^\oplus$, this being due to the $-I$ effect of fluorine, and trifluoroacetic acid is much stronger than acetic acid.

5. The high basicity of guanidine is attributed to the fact that its conjugate acid



¹ For a detailed study of this question the reader is referred to a review article by R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967).

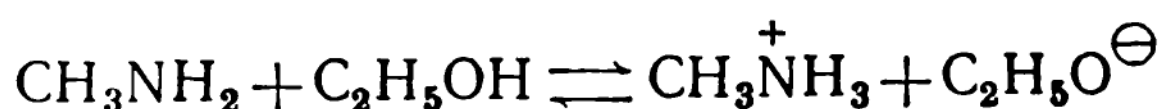
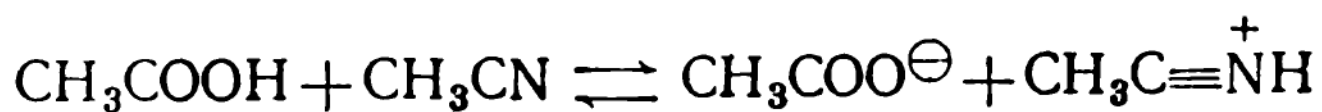
is weak due to the charge being delocalized at the nitrogen atoms (the +M effect of the NH_2 groups).

6. See J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, New York, 1965, page 651.

7. Because of the outer electronic shell of the central atom being incomplete. For more detail see D. J. Cram and G. S. Hammond, *Organic Chemistry*, 2nd ed., McGraw-Hill, 1964, page 217.

8. See D. J. Cram and G. S. Hammond, *Organic Chemistry*, 2nd ed., McGraw-Hill, 1964, page 205.

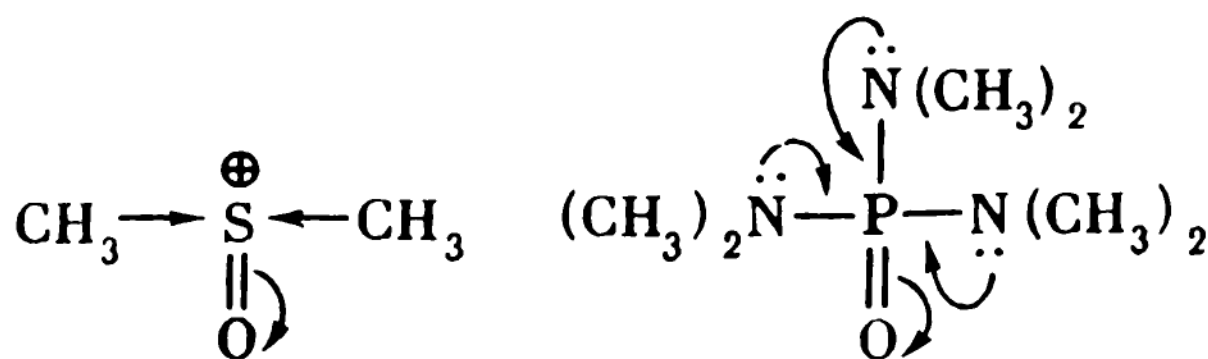
9. The dissociation constant depends on the acidity and basicity of the solvent participating in proton equilibria, for example,



and the values of K_a and K_b are therefore given for a definite solvent (usually water) at a definite concentration and temperature. Polar and readily polarizable solvents strongly solvate ions, which facilitates dissociation; the high dielectric constant (ϵ) of the solvent also contributes to dissociation.

10. In benzene, acetic acid dissociates to an immeasurably small degree, and in diethylamine the degree of dissociation is higher than in water (due to the higher basicity of the solvent).

11. Potassium *tert*-butylate is a stronger base than potassium methoxide because of the lower stability of the *tert*-butyl anion (the +I effect of the alkyl groups). The maximum basicity will be observed in solvents that strongly solvate the potassium cation and weakly solvate the alkoxyl anion, that is, in dimethylsulphoxide and especially in hexamethapole. These solvents



possess high basicity, i.e., the ability to solvate cations (the negative charge is localized on the oxygen atom) and a

low tendency for solvating anions since the positive charge is delocalized.

12. One of the methods of estimating the sign and magnitude of the inductive effect is to compare the dissociation constants of substituted and unsubstituted organic acids. Another method consists in comparing the dipole moments of various compounds that are derivatives of the same hydrocarbon (for example, CH_3Cl , CH_3NO_2 , CH_3CN). For more detail see J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, New York, 1965 and C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, Chapter III.

13. The mesomeric effect can be estimated by the difference between the dipole moment of a saturated compound and that of an α -, β -unsaturated compound having an analogous structure. For example,

$$\left. \begin{array}{ll} \text{C}_2\text{H}_5\text{Cl} & \mu = -2.05\text{D} \\ \text{CH}_2=\text{CHCl} & \mu = -1.44\text{D} \end{array} \right\} \Delta = +0.61\text{D}$$

This estimate however is semiquantitative since the quantity Δ includes the electrostatic polarizing effect on a double bond; it should also be taken into account that the electronegativity of an sp^2 -hybrid carbon atom is higher than that of an sp^3 -hybrid carbon atom. For more detail see C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, Chapter III. For the use of the constant σ for estimating the electronic effect of the substituent in the benzene ring, see J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, New York, 1965, page 956. Information on the use of the difference of the constants σ_{para} and σ_{meta} for estimation of the mesomeric effect can be found in C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, Chapter III.

14. The methoxy group is capable of exhibiting a $-I$ and a $+M$ effect.

15. The inductive and mesomeric effects of the halogens increase in the following series: $\text{I} < \text{Br} < \text{Cl} < \text{F}$ (the signs of the effects are reversed); in the case of substituted benzoic acids the $+M$ effect is observed, and for substituted acetic acids, the $-I$ effect.

16. The nitro group in the *para* position is capable of exhibiting the $-I$ and $+M$ effects, and in the *meta* position only the $-I$ effect is observed.

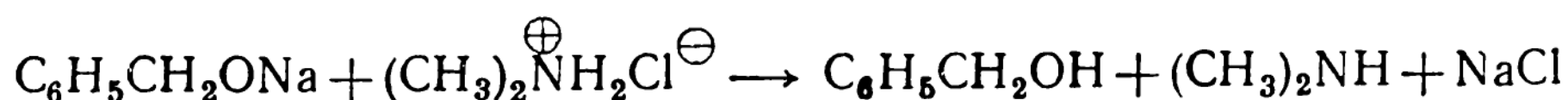
17. This method of separating the products of nitration of dimethylaniline is based on the difference in the basicity of the amines (compare the $-I$ and $-M$ effects).

18. $p\text{-CH}_3\text{O} > p\text{-CH}_3 > p\text{-Cl} > p\text{-Br} > m\text{-Br} > m\text{-NO}_2 > p\text{-NO}_2$. (Consider the donor and acceptor properties of the substituents.)

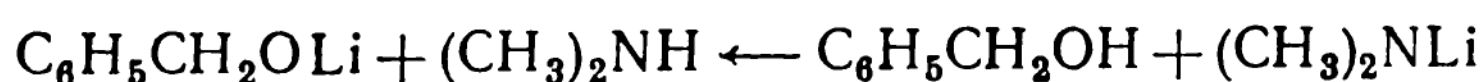
19. To answer the questions *a* through *f*, use the effects of the groups (see Introduction to this chapter). Information that may be used to check the dissociation constants of many substituted benzoic acids can be found in C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, Chapter XIV. See also D. J. Cram and G. S. Hammond, *Organic Chemistry*, pages 204 and 206.

20. The properties that are of primary importance to a nucleophilic reagent, apart from its basicity, are high polarizability and steric factors.

21. In order to arrange the compounds according to their basicity, one should consider in which direction the equilibrium of the reaction of distribution of a proton between two bases is shifted (i.e., the equilibrium between the bases and their conjugate acids). For example, one can compare $\text{C}_6\text{H}_5\text{CH}_2\text{ONa}$ and $(\text{CH}_3)_2\text{NH}$:

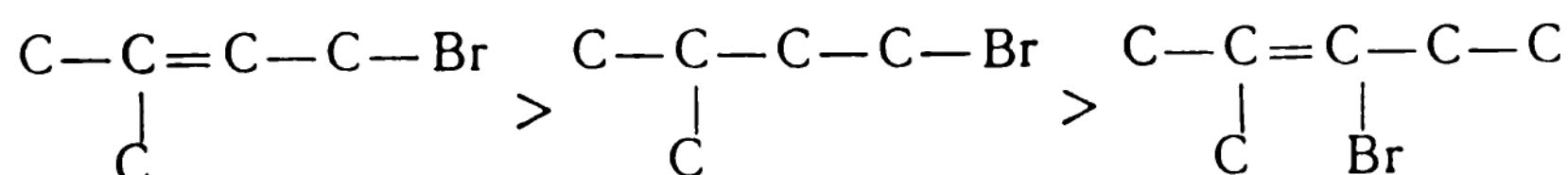


(i.e., the benzyolate anion is more basic than dimethylamine) or else $\text{C}_6\text{H}_5\text{CH}_2\text{OLi}$ and $(\text{CH}_3)_2\text{NLi}$:



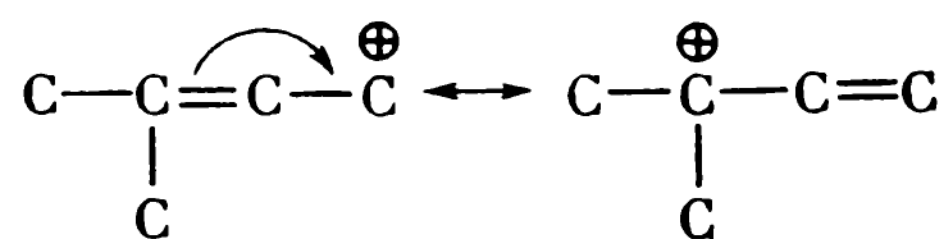
(i.e., the dimethylamide anion is a stronger base than the benzyolate anion). See also answer to Problem 19.

22. The mobility of the halogen in the compounds indicated changes in the following sequence:

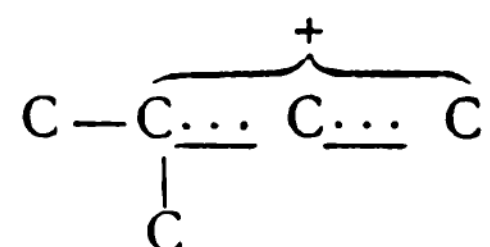


The bromine atom in 4-bromo-2-methylbut-2-ene exhibits the highest tendency for being displaced by nucleophilic reagents under both the S_N1 and S_N2 conditions.

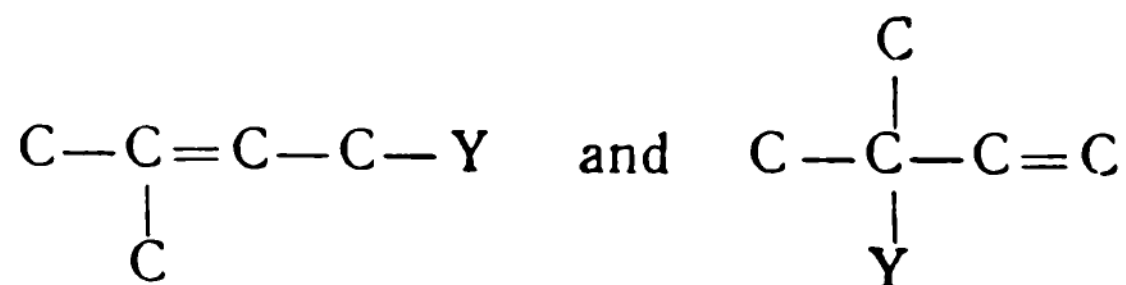
In the first case the heterolytic cleavage of the molecule into ions is easier due to the presence of a multiple bond which takes part in the distribution of the positive charge in the carbonium ion, thereby contributing to its stabilization:



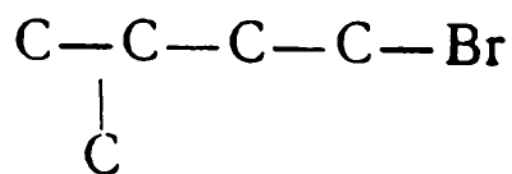
or



However, when the reaction is carried out under these conditions, nearly equal amounts of two substitution products are obtained:

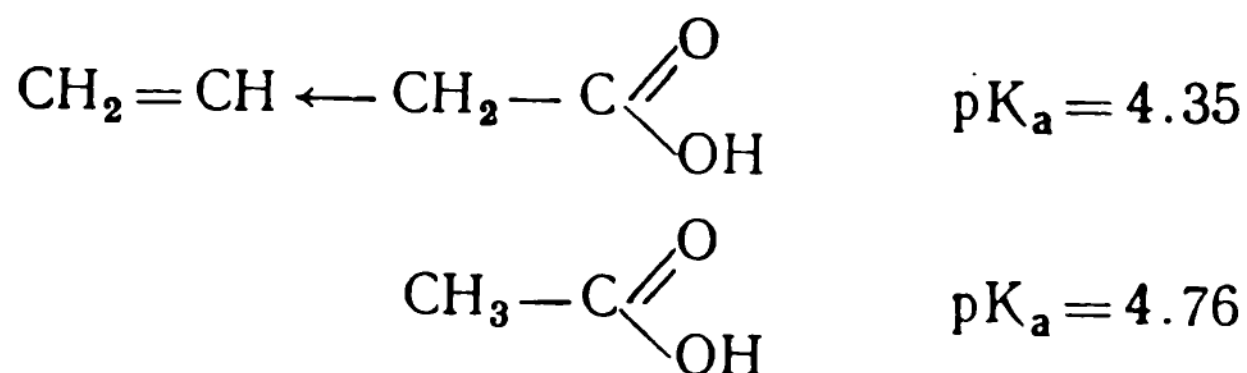


In the second case the bromine atom is more reactive than an alkyl halide of analogous structure:



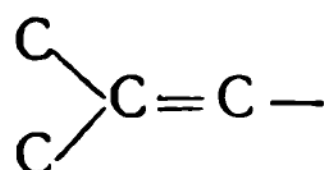
There are two reasons for this. It is known that the vinyl group shows a $-I$ effect, i.e., it possesses electron-accepting properties, though they are not very strong.

This can be confirmed by a decrease in the pK_a of vinylacetic acid as compared with acetic acid

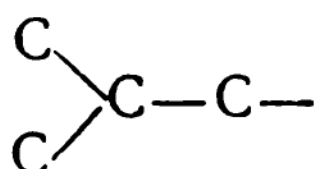


Therefore, in compounds of the type $\text{CH}_2=\text{CH}-\overset{\delta+}{\text{CH}_2}$, the magnitude of δ^+ on the carbon atom being attacked is higher than in propyl bromide, a circumstance which must speed up the reaction proceeding by the $\text{S}_{\text{N}}2$ mechanism.

Besides, the group



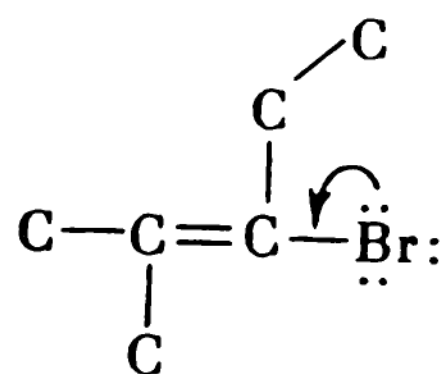
which has a planar structure exerts a lower shielding effect than the group



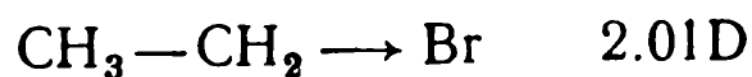
when the nucleophilic reagent attacks from the rear side of the molecule.

The lowest tendency of 3-bromo-2-methylpent-2-ene for nucleophilic substitution reactions is due to the presence of a $+M$ effect at the bromine atom.

The fact that the vinyl group, in which one of the carbon atoms is attached to the bromine atom, has electron-accepting properties causes shifting of the unshared pairs of p -electrons of the bromine atom (the shifting shown by an arrow):



This shifting can be detected through a comparison of the dipole moments of ethyl and vinyl bromides:

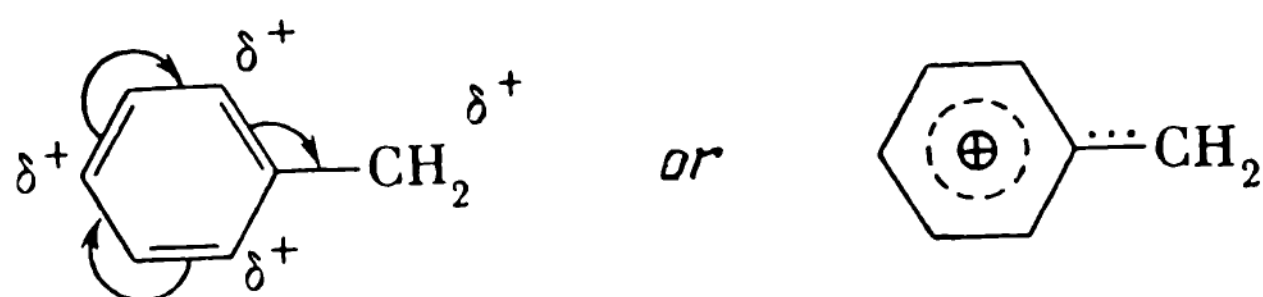


Since for the halogens the $-I$ effect is stronger than the $+M$ effect, the negative end of the dipole in vinyl bromide is invariably at the halogen atom, but the magnitude of δ^+ at the carbon atom being attacked is found to be considerably decreased and the bromine atom becomes attached somewhat

stronger than monocovalently to the vinyl group. This must result in a decrease of the reactivity of vinyl halides as compared with alkyl halides.

25. Benzyl chloride has a greater reactivity than cyclohexylchloromethane under both the S_N1 and S_N2 conditions.

In the first case, phenyl, like the vinyl group, participates in the distribution of the positive charge in the carbonium ion formed



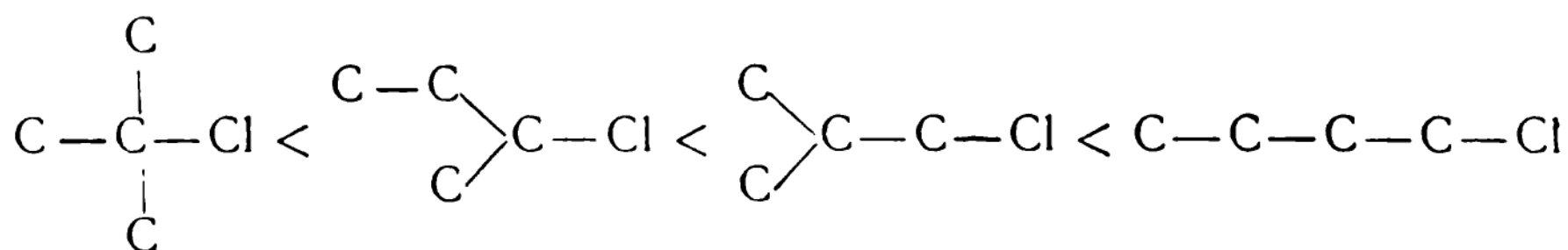
and in the second, according to the considerations given in answer to Problem 22, the magnitude of δ^+ for benzyl chloride will be higher and phenyl will exert a lesser shielding effect during the attack by the nucleophilic reagent.

27. The ease of hydrolysis of the indicated compounds changes in the following order: $R-I > R-Br > R-Cl$. This evidently depends on the magnitude of the energy of the $C-X$ bond, which is ruptured in substitution reactions:

$C-I$	45.5 kcal/mole
$C-Br$	54.0 kcal/mole
$C-Cl$	66.5 kcal/mole
$C-F$	107.0 kcal/mole

The increased nucleophilicity of iodine exerts an effect in the same direction.

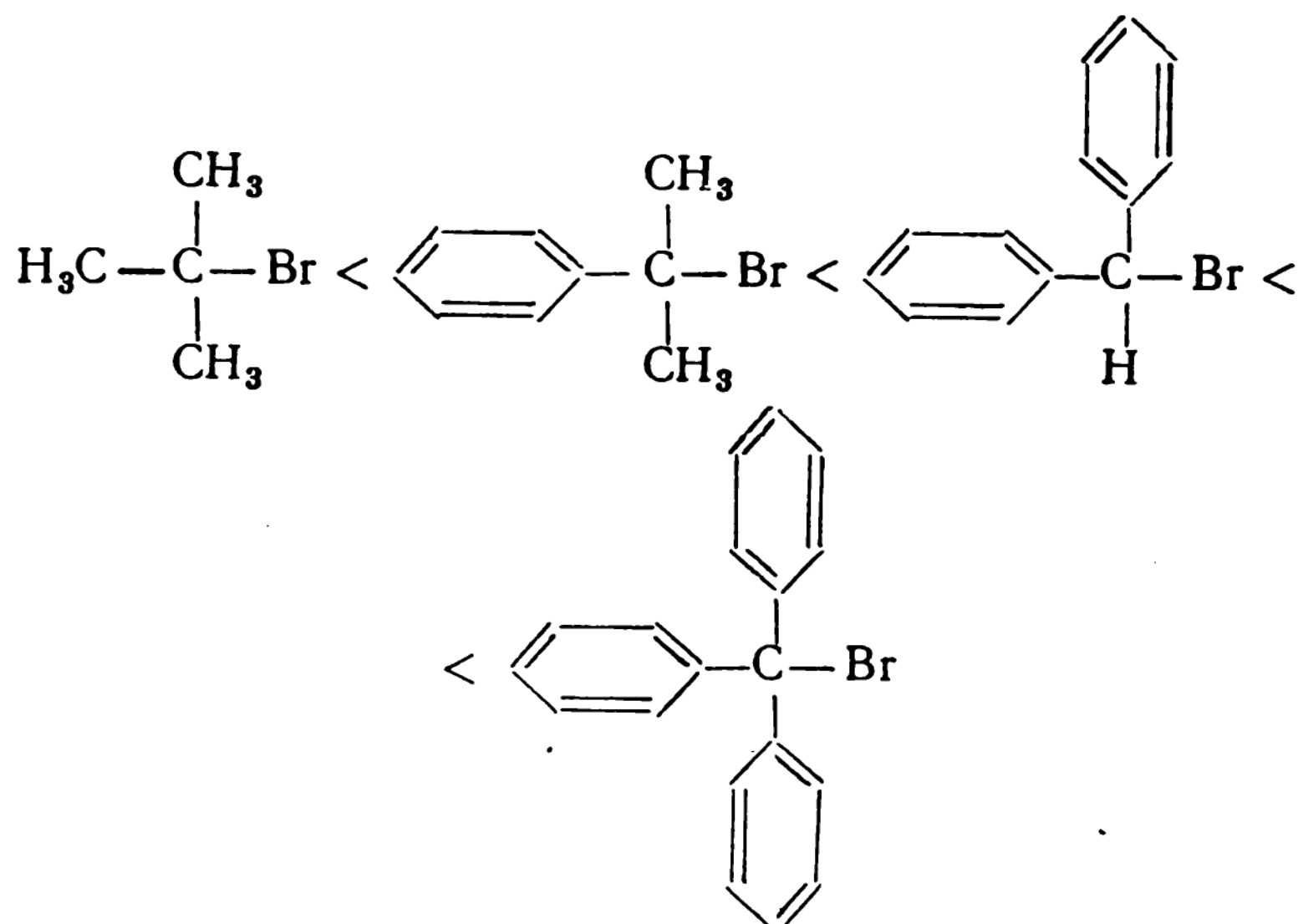
28. Isomeric chlorobutanes may be arranged in order of increasing reactivity in S_N2 reactions as follows:



The decisive factor in this case is the shielding effect of the alkyl groups. Since these groups possess electron-accepting properties, a lesser effect is exerted by a slight decrease of δ^+ at the carbon atom attacked by the nucleophilic reagent.

29. The reactivity of the indicated compounds in reactions proceeding by the S_N1 mechanism increases in the following

sequence:

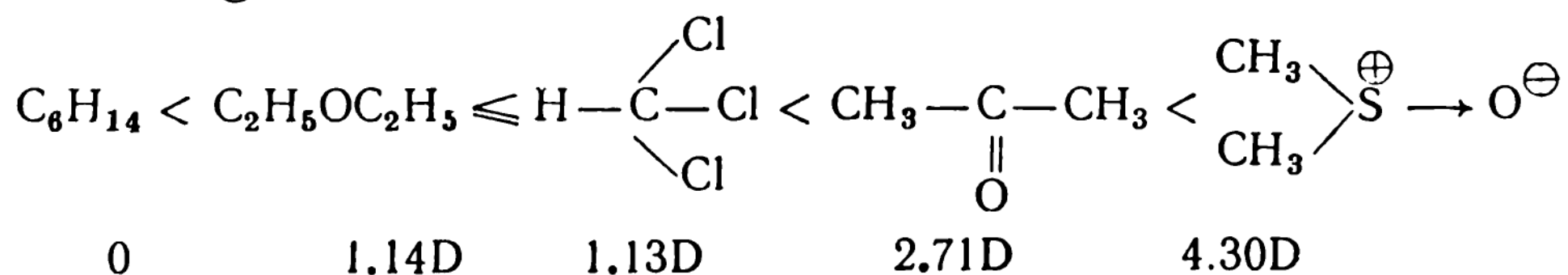


It depends on the ability of the groups attached to the central carbon atom to take part in the distribution of the positive charge in the carbonium ion formed at the first stage. The phenyl group possessing readily polarizable π -electrons has a stronger effect than the methyl group on the tendency of the substrate molecule to dissociate into ions.

31. The compound A is 4-bromobut-1-ene, B is 1-bromobut-1-ene, and C is 1-bromobut-2-ene.

32. The ability of solvents to solvate cations depends on the degree of concentration of excess electron density at any one atom in the molecule and it may be characterized by the dipole moment.

For the solvents in question this ability increases in the following order:

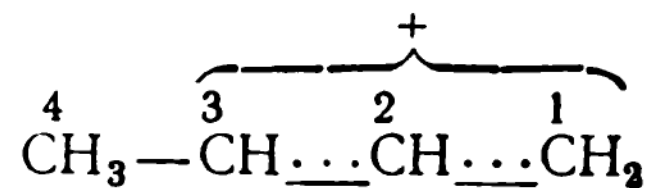


35. These data were obtained for reactions proceeding by the $\text{S}_{\text{N}}2$ mechanism. The rate of the reaction was slowed down by the shielding effect of the alkyl groups and by a certain decrease of the value of δ^+ at the attacked carbon atom.

38. The hydrolysis of ethyl bromide, which is a primary alkyl halide, must be carried out under conditions favourable for a reaction proceeding by the S_N2 mechanism through the action of alkali in aqueous-alcoholic solution. An alcohol cannot be made in this way from *tert*-butyl bromide because in this case the elimination reaction involving the formation of isobutylene is predominating. The replacement of $-\text{Br}$ in 2-bromo-2-methylpropane by an $-\text{OH}$ group can be accomplished by boiling it with water, and binding the HBr formed with the aid of an organic base.

40. When crotyl chloride is hydrolysed with an aqueous solution of potassium hydroxide, the reaction proceeds predominantly by the S_N2 mechanism and therefore the major part of the products formed is crotyl alcohol, $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_2\text{OH}$.

The hydrolysis with water results in the formation of nearly equal amounts of crotyl alcohol and but-1-en-3-ol because in this case the reaction proceeds by the S_N1 mechanism and the substitution reaction itself is preceded by the heterolysis of the starting material, which leads to a carbonium ion

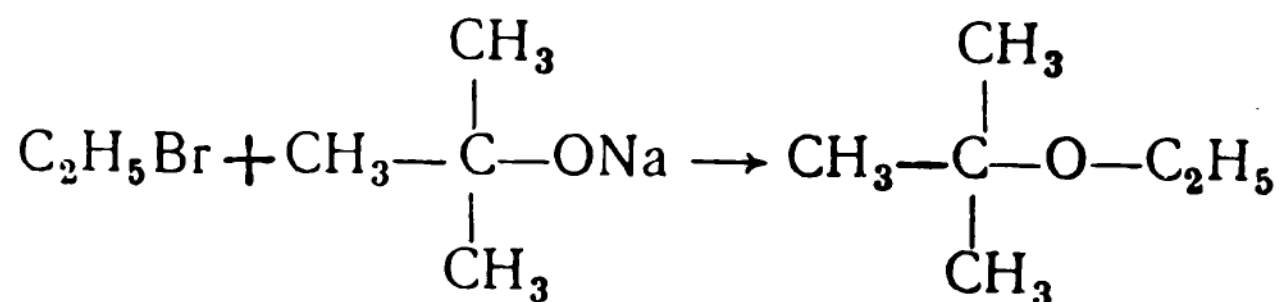


in which the carbon atom 1 or 3 may be attacked by water with equal probability.

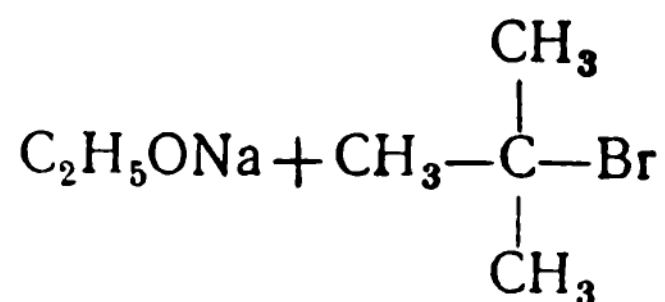
42. Moist benzene < aqueous acetone < aqueous alcohol < water < aqueous formic acid.

44. See answer to Problem 35.

46. Ethyl-*tert*-butyl ether is conveniently made through the action of sodium *tert*-butoxide on a solution of ethyl bromide in an aprotic solvent:



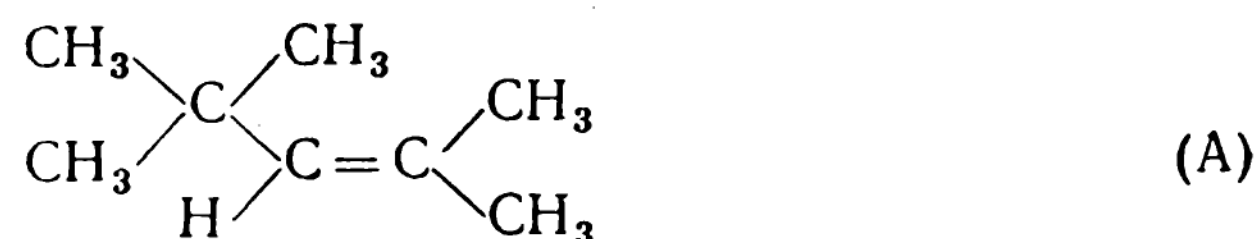
The reverse combination of the initial reagents



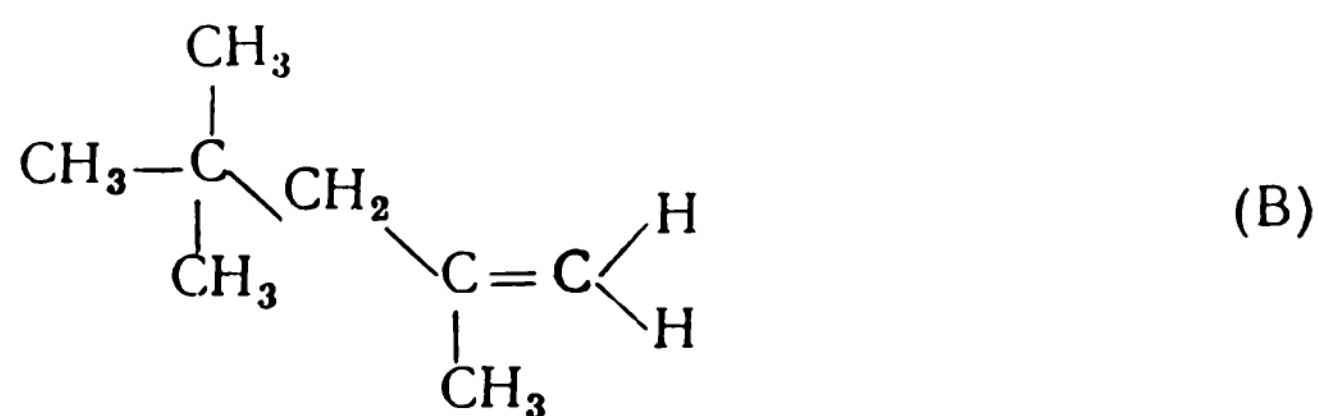
is excluded in this case since sodium ethoxide acting as a strong base will completely convert tertiary butyl bromide, which is more prone to an elimination reaction, into isobutylene. In the former case the yield is also low because of the elimination reaction leading to ethylene.

52. The difference in the reaction rates may be accounted for by the fact that the nucleophilic activity of $\text{C}_4\text{H}_9\ddot{\text{S}}:\oplus$ is much higher than that of the butylate anion. The yield of thioether however is higher because $\text{C}_4\text{H}_9\ddot{\text{S}}:\oplus$ is a weaker base and in this case no elimination reaction with the formation of butylene is involved.

54. When the reaction of elimination of 4-bromo-2,2,4-trimethylpentane is carried out, instead of the branched olefin



which might be expected according to the Zaitsev rule, there is mainly formed olefin B with a terminal double bond since the hydrogen of the CH_3 group is more available for being removed by a nucleophile:



Besides, this result is explained as follows: in the resulting olefin all the substituents must be positioned in a single plane. As far as the formation of olefin (A) is concerned such an arrangement is hindered by the mutual repulsion of the bulky *tert*-butyl group and the methyl group in the *cis*-position.

58. For 2-nitropropane to be prepared from isopropyl bromide, which is capable of reacting by the $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ mechanisms, use must be made of a polar aprotic solvent incapable of causing the initial compound to dissociate into ions (for example, dimethylformamide). The nitrite anion has

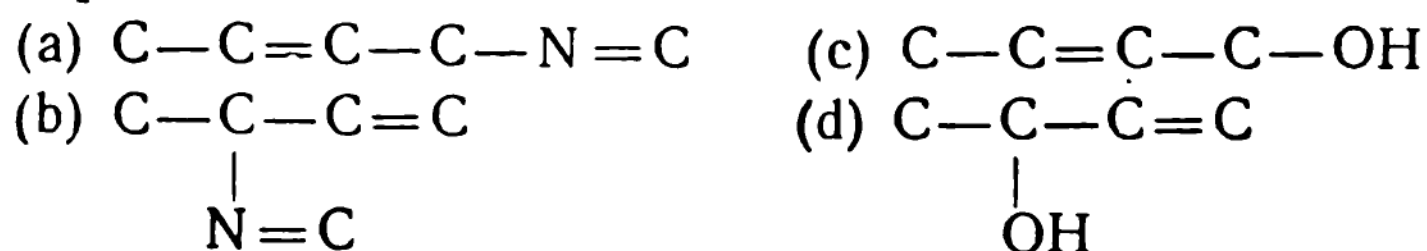
the structure $\text{:}\ddot{\text{O}}\cdots\text{N}\cdots\ddot{\text{O}}\text{:}^\ominus$. All the three atoms in it (one nitrogen and two equivalent oxygens) possess unshared pairs of electrons, but the nucleophilic strength of the nitrogen atom is greater. Therefore, when the reactions are carried out under conditions most favourable for the $\text{S}_{\text{N}}2$ mechanism, the nucleophile $\text{NO}_2^\ominus$ will attack the substrate through the nitrogen atom to form a nitro compound.

But when the reaction is carried out, say, in water which causes the starting isopropyl bromide to dissociate into ions, or when $\text{Ag}^\oplus$ is used as a catalyst, the resulting carbonium ion will attack the nitrite anion at the site of highest electron density, namely, at one of the oxygen atoms more electronegative than nitrogen, the reaction product being isopropyl nitrite.

59. See answer to Problem 58.

61. In water, crotyl chloride reacts predominantly by the $\text{S}_{\text{N}}1$ mechanism.

Taking into account the considerations given in answers 40 and 58, one can say that the interaction of an aqueous solution of crotyl chloride with potassium cyanide yields four products:

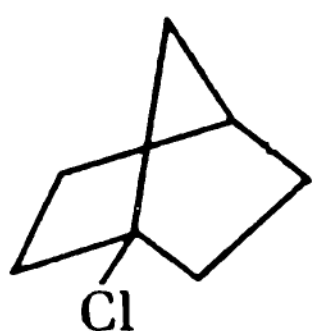


But when the reaction is conducted in dimethylsulphoxide or hexane, it proceeds practically uniquely by the $\text{S}_{\text{N}}2$ mechanism with the formation of a nitrile:

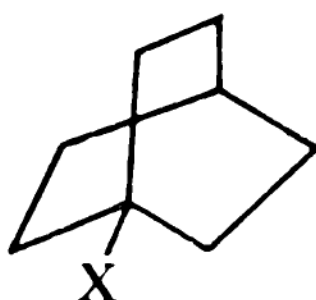


65. It should be taken into account that when the reaction follows the $\text{S}_{\text{N}}1$ mechanism, the transition-state carbonium ions must have a planar or nearly planar structure of the reaction centre. It is therefore obvious that in the case of very rigid systems of the 1-chloroapocamphane (IV) type the exchange of chlorine will be considerably hindered. Indeed, no reaction takes place when (IV) is boiled for 48 hours in an aqueous-alcoholic solution of silver nitrate. For comparison, it should be noted that aliphatic or alicyclic chlorides (for instance, cyclohexyl or cyclopentyl chloride) exchange chlorine rather rapidly under these conditions. At

the same time it is important to take into account that increasing the size of the ring in bi- and polycyclic systems makes S_N1 type reactions possible since in this case the formation of a planar or nearly planar carbonium-ion centre is facilitated. This can be illustrated by the behaviour of the derivatives of bicyclo[2,2,2]octane (III) or adamantane (II):



(IV)



(III)

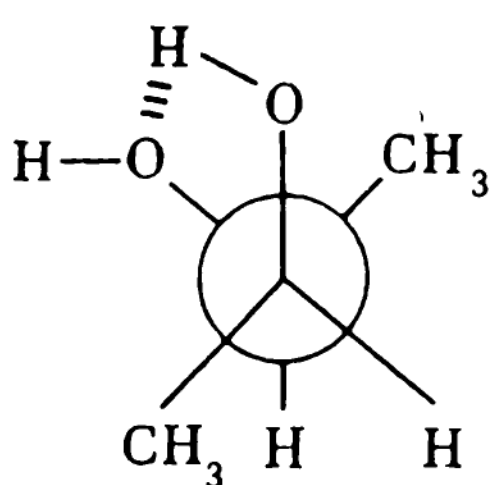


(II)

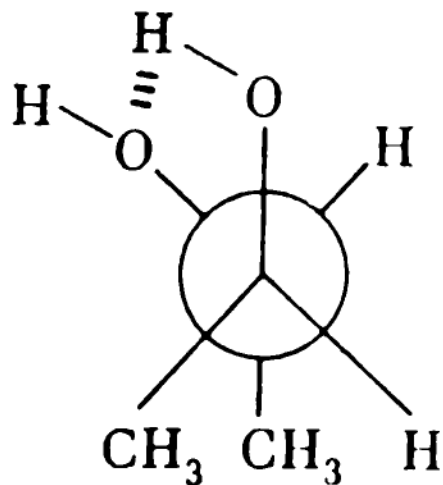
The compounds (II) and (III) appear to be more reactive under the conditions indicated, though their ability to engage in S_N1 type reactions is still lower than that of aliphatic compounds. It is interesting that 1-substituted adamantanes (II) engage in S_N1 -type reactions much more rapidly than 1-substituted bicyclo[2,2,2]octanes (III). Their reaction rates differ by more than 3 orders of magnitude. This difference is ascribed to the scattering of the carbon atoms C_1 and C_4 in (III), which impedes the formation of a planar carbonium-ion centre at C_1 .

66. See the previous answer.

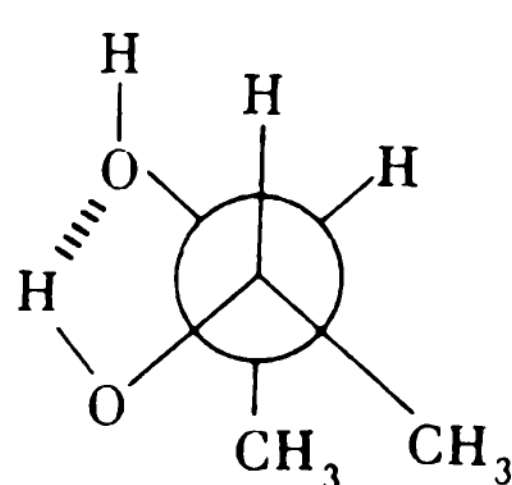
67. An intramolecular hydrogen bond appears in stereoisomeric butanediols when the hydroxyl groups are close to each other. In the case of a *dl*-isomer the formation of a hydrogen bond can be represented by formula (V) and in the case of a *meso*-isomer, by formula (VI) or (VII):



(V)



(VI)

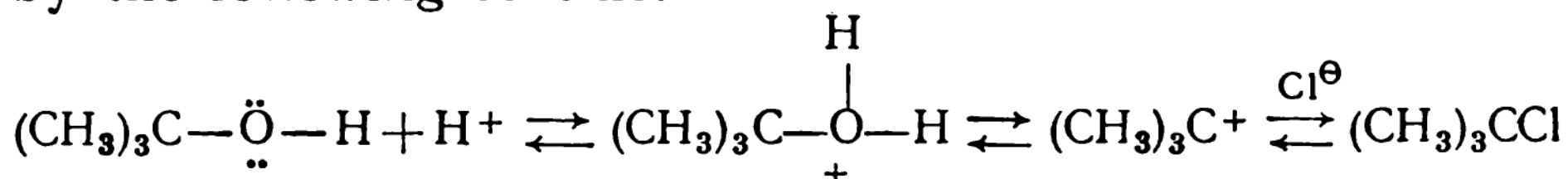


(VII)

As seen from these schemes, the conformations (VI) and (VII) must be the least stable since they involve steric interaction

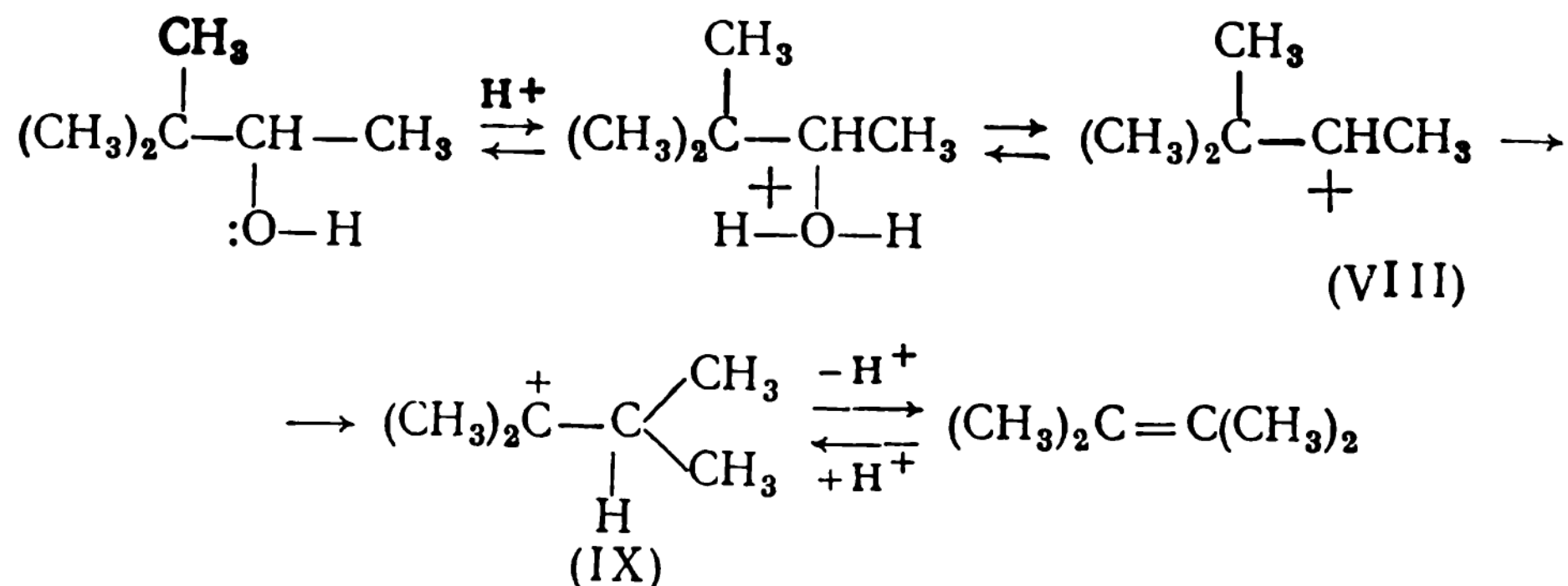
(repulsion) of methyl groups, which weakens the hydrogen bond.

68. The difference in the behaviour of *n*-butyl and *tert*-butyl alcohols under the conditions specified is attributed to their ability to form carbonium ions. The exchange of the hydroxyl group in *tert*-butyl alcohol may be represented by the following scheme:



Concerning the factors responsible for the stability of carbonium ions see A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 2, Moscow, Izd. Khimiya, 1970; see also J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

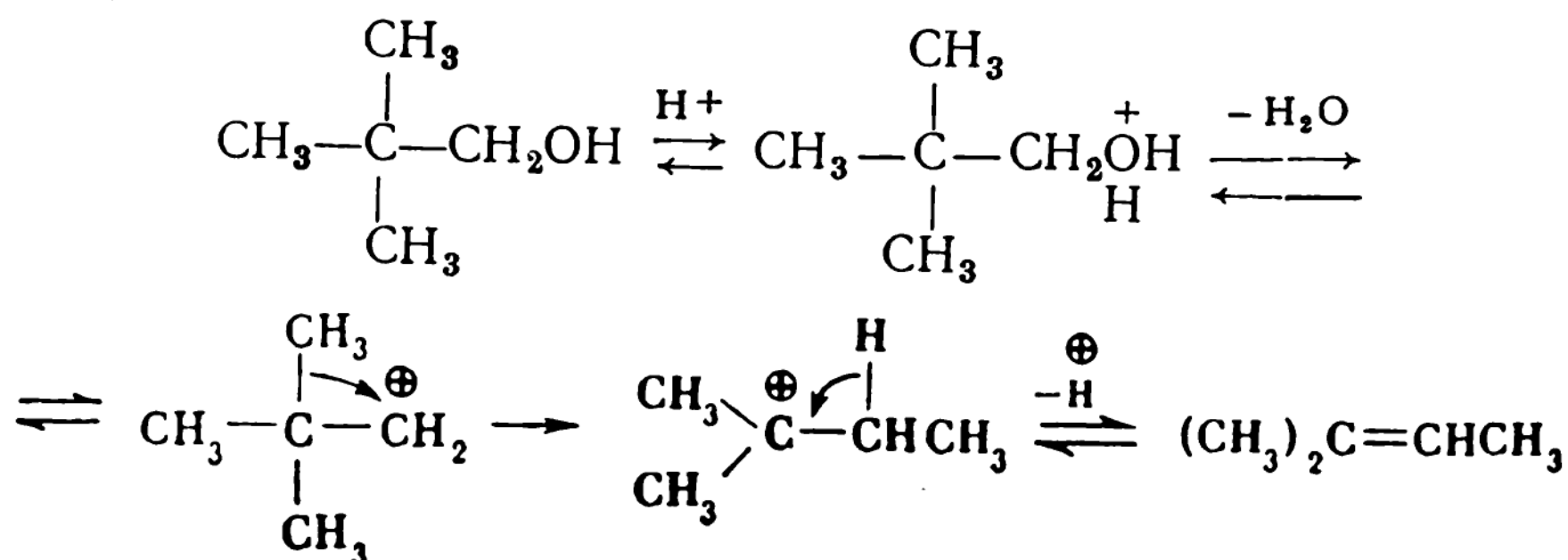
69. Under the conditions of acid dehydration there takes place the coordination of the proton of the mineral acid across the oxygen atom of the hydroxyl group. The resulting hydroxonium ion is capable of losing the elements of water and being converted into a methyl-*tert*-butylcarbonium ion (VIII) which is isomerized into a more stable ion (IX), this ion being stabilized owing to the proton being ejected as tetramethylethylene:



The stage at which the carbonium ion (VIII) is formed is analogous to the corresponding step, say, in the reaction of *tert*-butyl alcohol with hydrobromic acid, but the structural features of the ion (VIII) are favourable for rearrangement into a more stable ion (IX), which occurs prior to the attack by a nucleophile. For more detailed information on the trans-

formations of carbonium ions, see A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 2, page 575; see also J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

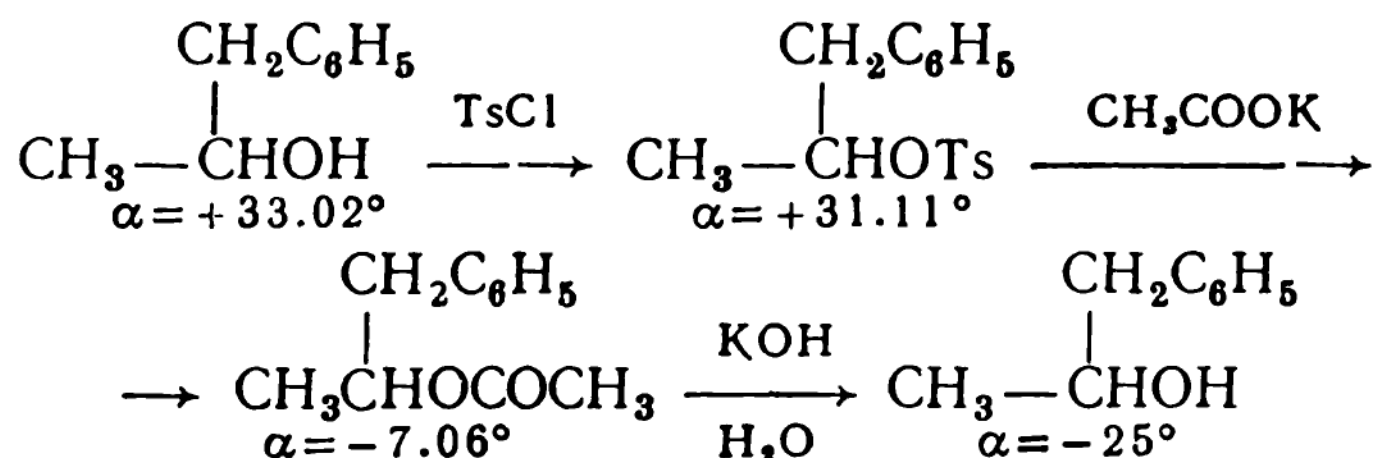
70.



See answers 68 and 69.

71. In the scheme shown (+)-1-phenylpropan-2-ol is converted into ethyl ether in two ways. The synthesized samples differ in optical activity. This means that at least at one of the four stages the configuration of the asymmetric centre has been inverted. If it is taken into account that at stages (1)-(3) the asymmetric centre remains intact (the reactions involve only the —O—H or —O—K bonds and not the C—O bonds), then one must assume that the configuration of the asymmetric carbon atom has been changed at stage (4).

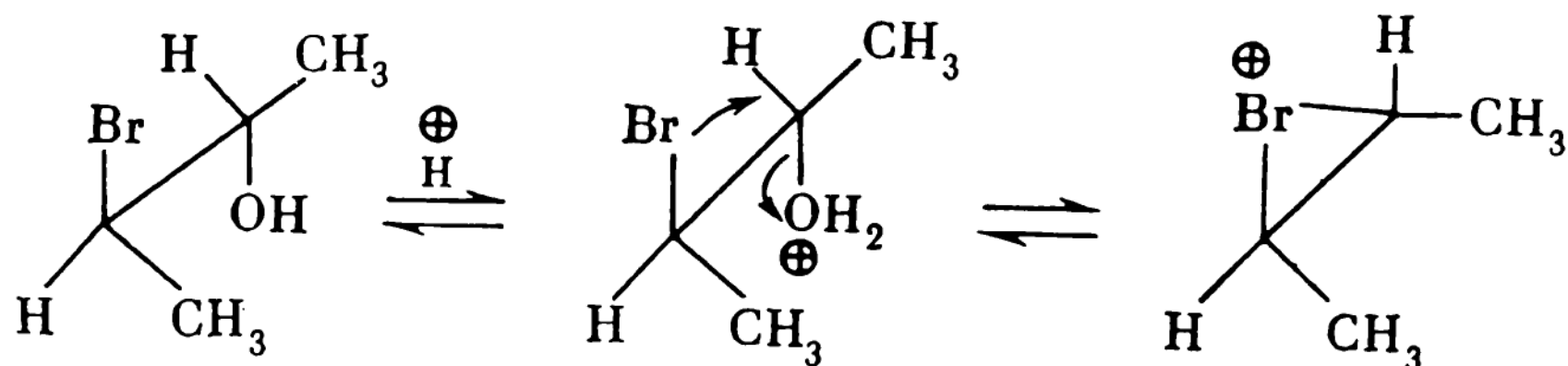
72.



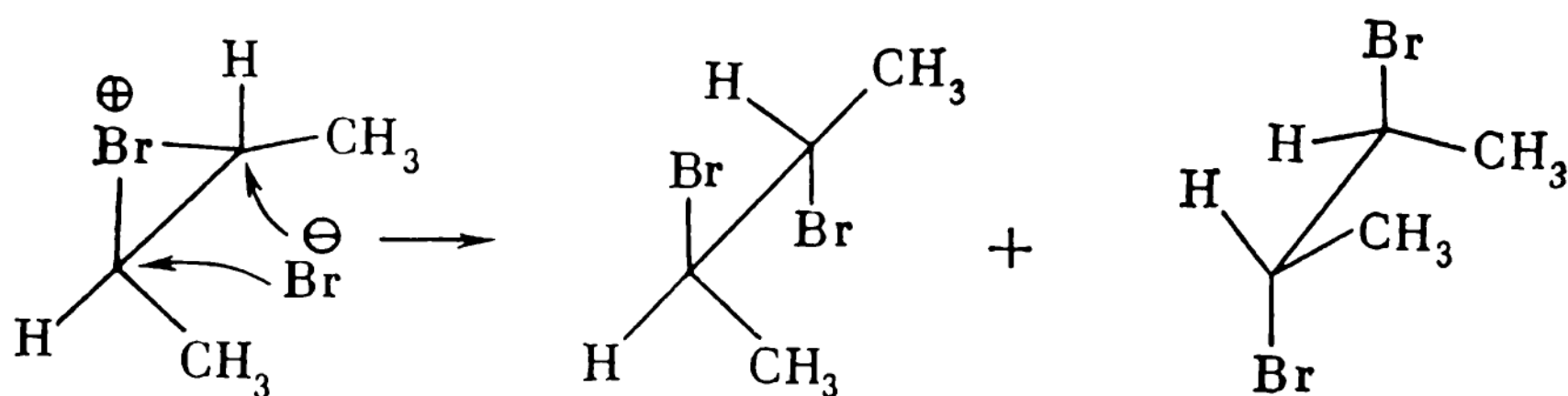
For discussion of similar conversions see the previous answer.

73. The conversion of optically active *erythro*- and *threo*-3-bromobutan-2-ols into *meso*- and *dl*-2,3-dibromobutane, respectively, proceeds with retention of the configuration of the reaction centre. This retention of the configuration however cannot be accounted for on the basis of the simplest conceptions of the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms. Indeed, one might have expected the formation of a mixture of *threo*-

and *erythro*-dibromides (by the S_N1 mechanism) from both bromohydrins and accordingly of a mixture of *threo*- and *erythro*-dibromides from *erythro*- and *threo*-bromohydrins (by the S_N2 mechanism). The following scheme has been proposed to account for these results: the starting bromohydrin (*erythro*- and *threo*-) adds a proton to form a hydroxonium ion in which the loss of the elements of water is accompanied by the attack of the neighbouring bromine atom (inversion of the configuration of the reaction centre):



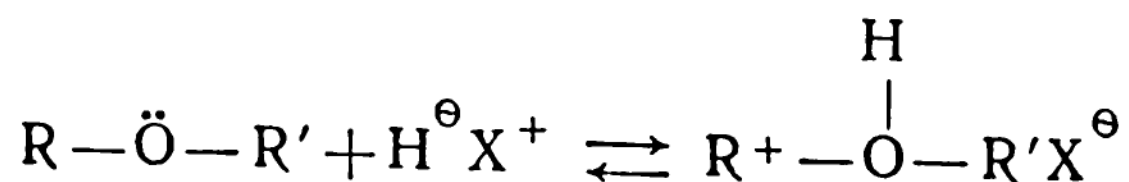
The attack of the bromide ion on any carbon atom of the symmetrical bromonium ion (second inversion of the configuration) leads to racemic *threo*-2,3-dibromobutane:



Thus the retention of the configuration in the reaction product is associated with double inversion of the configuration during the reaction.

75. The higher activity of hydriodic acid in reactions of cleavage of ethers is ascribed to the fact that the iodide anion is the strongest nucleophile under acidic conditions.

76 and 77. The reactions of ethers with strong mineral acids proceed in the same way as the corresponding reactions of alcohols. The presence of free electron pairs at an oxygen atom is responsible for the basic properties of ethers. Therefore the first step in the reaction of ethers with strong acids involves their protonation with the formation of hydroxonium ions:

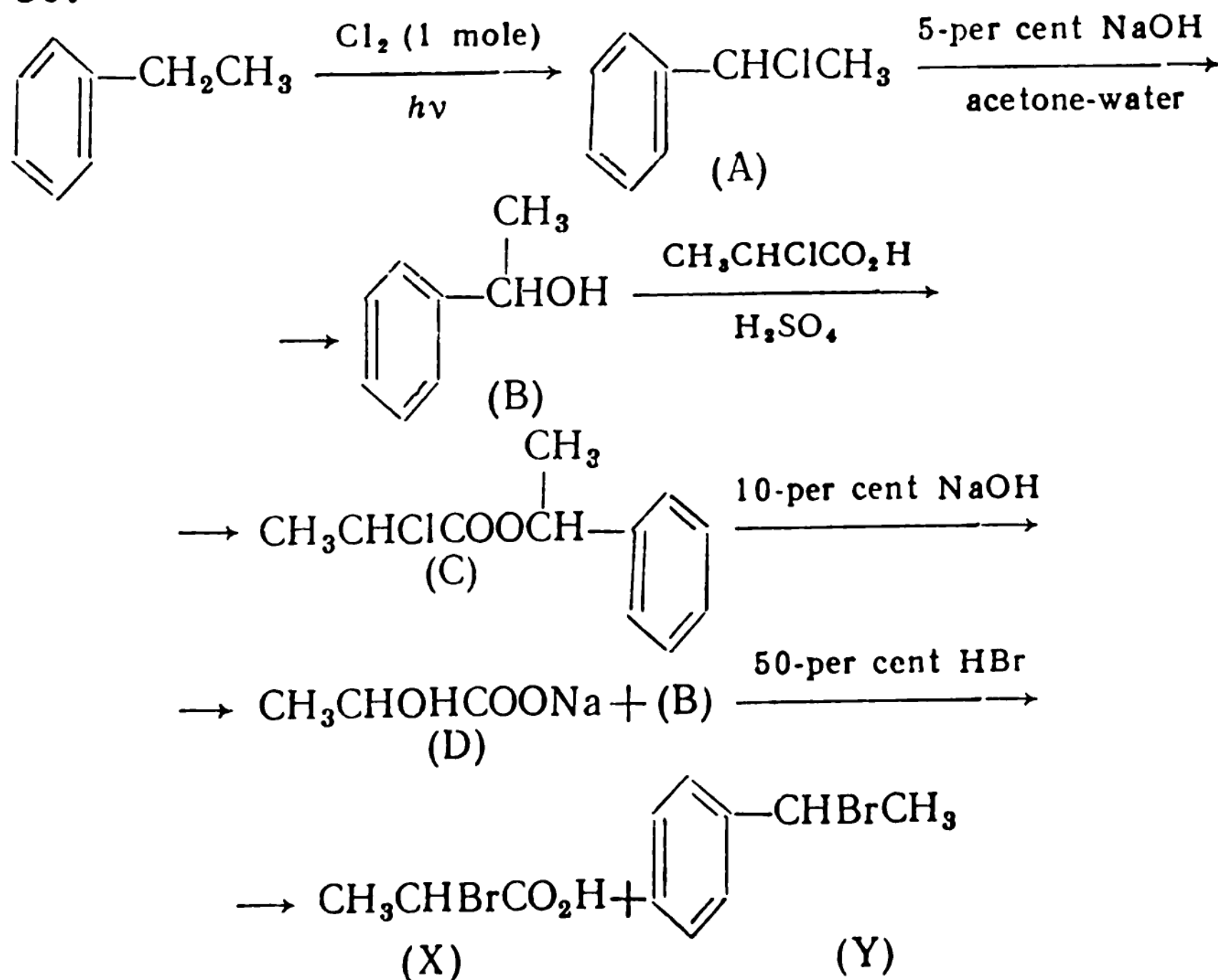


Depending on the structure of R and R' and the reaction conditions (the basicity and nucleophilicity of the anion, the nature of the solvent and other factors), hydroxonium ions of this kind may enter into the substitution (S_N1 or S_N2) or elimination reactions. To solve the problems of this section one must therefore take account of all these possibilities. For detailed consideration of the chemical properties of ethers see A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 1, Moscow, Khimiya, 1969, pages 120-128; see also J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

78. The fact that the oxide ring is preferably broken at the least substituted carbon atom is evidence of a bimolecular reaction. See Problems 119, b and c, and 127.

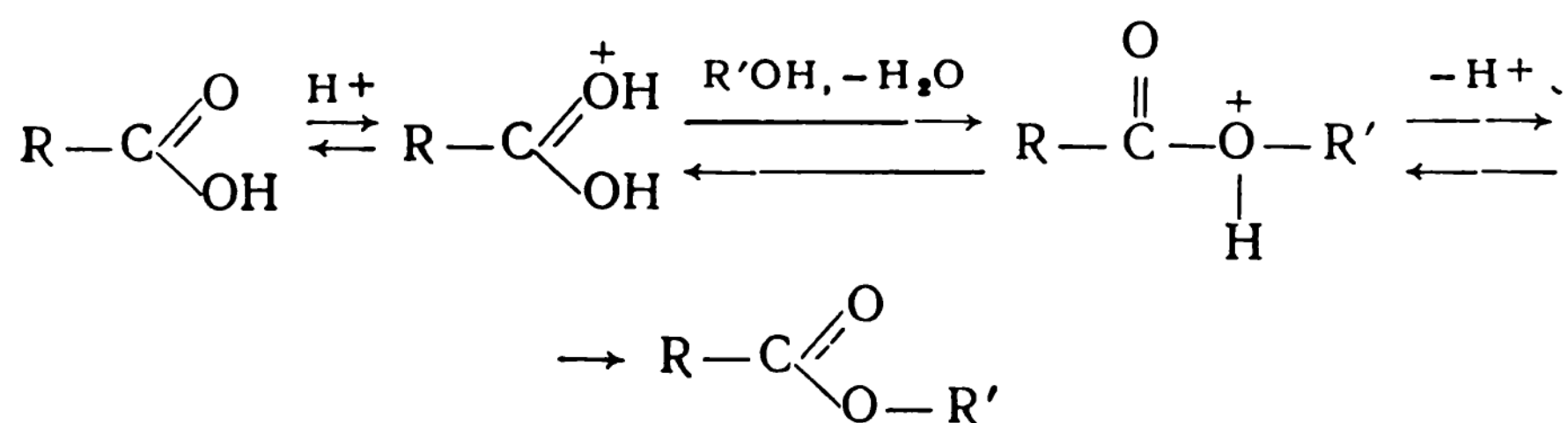
79. Under acidic conditions α -oxides react in a protonated form both by the S_N1 and the S_N2 mechanism. The reaction usually proceeds via the most substituted carbon atom of the oxide ring. Thus, when the neutral (see the previous problem) conditions are changed to acidic, the direction of the opening of the oxide ring is changed.

80.



81. The best result (as to the degree of conversion and the absence of side reactions) is obtained when use is made of diazomethane. To substantiate this answer, the concepts of the mechanism of ester formation must be made use of.

82. The indicated order of decreasing rate of esterification of acids is evidence of the strong effect of steric hindrances in the presence of substituents at α -carbon atom. These data are in good agreement with the mechanism of esterification involving the nucleophilic attack of an alcohol molecule on the electron-deficient centre of the carboxyl group:



83. For a discussion of this question see O. Reutov, *Theoretical Principles of Organic Chemistry*, Mir Publishers, Moscow, 1968.

84. For the behaviour of ketene with respect to the indicated reagents see J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965, Chapter 15.

93. (a) Propylene is chlorinated in the light at elevated temperature (see Chapter 2). The resulting allyl chloride is saponified.

(b) To propylene, in the presence of a peroxide or on irradiation with ultraviolet light, there is added, contrary to the Markovnikov rule, hydrogen bromide. The resulting *n*-propyl bromide reacts, as a primary alkyl halide, with alkali metal cyanides by the $\text{S}_{\text{N}}2$ mechanism even in such solvents as alcohol; no undesirable isonitriles are practically formed. The thus prepared butyronitrile is hydrolysed to butyric acid.

(c) The addition of hydrogen bromide to propylene yields isopropyl bromide. This compound is allowed to react with sodium iodide dissolved in acetone (the Finkelstein reaction).

(d) To prepare nitroalkanes from primary and secondary alkyl bromides and iodides the corresponding halides are allowed to react with sodium and potassium nitrites in sol-

vents such as dimethylformamide or dimethylsulphoxide. When secondary halides are used to increase the solubility of the nitrite, urea is added to dimethylformamide.

Isopropyl bromide (for its preparation see answer to Problem 93c) can be used in this way to synthesize 2-nitropropane. It should be noted that, in addition to the nitro compound, there is always formed the corresponding ester of nitrous acid.

The synthesis can be carried out in the absence of solvents. To do this, silver nitrite (it is insoluble in water and is prepared by mixing solutions of sodium nitrite and silver nitrate) is thoroughly mixed with a threefold amount of pure fine-grained sand and the corresponding alkyl iodide is added to the mixture.

When this method is used, isopropyl iodide yields a mixture of equal amounts of 2-nitropropane and isopropyl nitrite (the total yield is 60 per cent). The latter boils at a temperature 70°C lower than the other component and is therefore easily separated by distillation.

(e) Isopropyl nitrite (for its preparation together with 2-nitropropane see answer 93d) can also be synthesized from isopropyl alcohol by the action of sodium nitrite and hydrochloric acid.

94. (a) First, isobutyl alcohol should be dehydrated and then water is added to the resultant isobutylene in the presence of sulphuric acid. The reaction product—*tert*-butyl alcohol—is treated with concentrated hydrochloric acid.

(b) Isobutylene (for its preparation see the previous answer) is chlorinated in the light at increased temperature. The methallyl chloride (1-chloro-2-methylprop-2-ene) formed is treated with a suspension of a nitrite in absolute ether.

(c) To a solution of methallyl chloride (see answer 94b) in acetone is added crystalline sodium sulphide. The reaction is brought to completion by boiling the mixture using a reflux condenser.

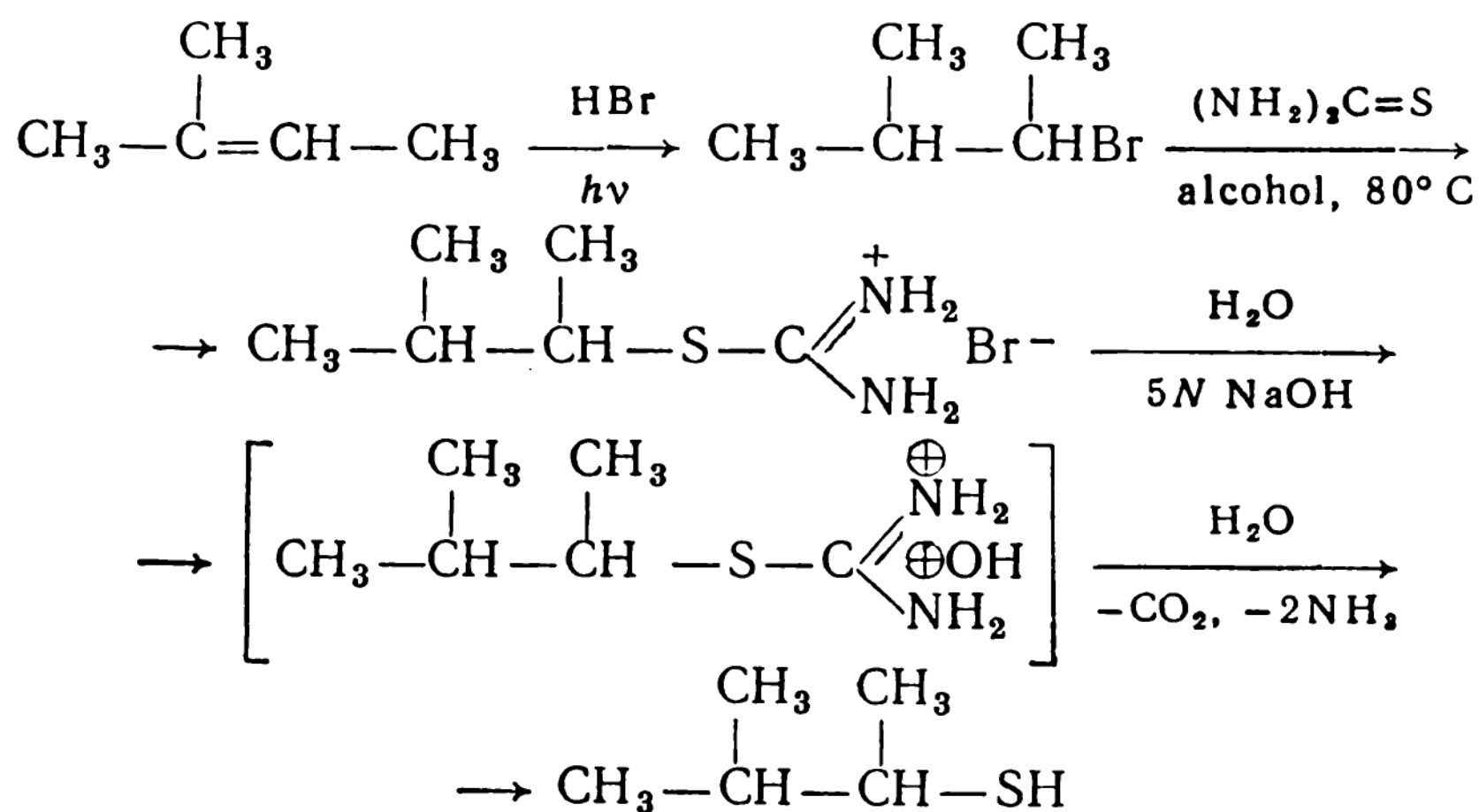
95. (a) To cyclohexanol is added dried red phosphorus and then, on mixing, dry bromine (calculate the amounts of reagents required). The cyclohexyl bromide formed is heated in diglyme (diethylene glycol dimethyl ether) with well powdered sodium cyanide (see answer 93b). The nitrile of

cyclohexanecarboxylic acid thus prepared is subjected to hydrolysis in acid or alkaline medium.

(b) Cyclohexanol is dehydrated and the cyclohexene formed is brominated into the allyl position with bromosuccinimide. The 3-bromocyclohexene thus produced is then hydrolysed.

(c) 3-Bromocyclohexene is converted by the action of sodium cyanide into the corresponding cyanide (see answers 93b and 95a) which is then hydrolysed.

96. To 2-methylbut-2-ene is added, contrary to the Markovnikov rule, hydrogen bromide. The 3-bromo-2-methylbutane formed is heated with an alcoholic solution of thiourea. The resulting salt of S-alkylisothiuronium is hydrolysed with alkali into a mercaptan.



97. First, chloroacetic acid is prepared from methanol. The scheme for the synthesis is as follows: methanol $\xrightarrow{\text{SO}_2\text{Cl}_2}$ dimethyl sulphate $\xrightarrow{\text{KCN}}$ acetonitrile $\xrightarrow[(\text{H}_2\text{SO}_4)]{\text{H}_2\text{O}}$ acetic acid $\xrightarrow[h\nu]{\text{Cl}_2}$ chloroacetic acid $\xrightarrow{\text{KCN}}$ cyanoacetic acid $\xrightarrow[\text{H}^+]{\text{CH}_3\text{OH}}$ methyl cyanoacetate.

98. (a) First, the sodium salt of cyanoacetic acid is prepared: ethyl alcohol $\xrightarrow{[\text{O}]}$ acetic acid $\xrightarrow[h\nu]{\text{Cl}_2}$ chloroacetic acid $\xrightarrow[(2) \text{ NaCN}]{(1) \text{ Na}_2\text{CO}_3}$ sodium salt of cyanoacetic acid.

The salt of cyanoacetic acid isolated is treated with absolute alcohol and sulphuric acid. The reaction (the alcoholysis of the nitrile) proceeds via the stage of formation of iminoester, which is readily converted on hydrolysis into diethyl malonate.

Malonic ester is produced on an industrial scale by this method.

(b) Ethyl alcohol (ethanol) is converted to ethyl bromide. One of the following three methods is most often employed: (1) One mole of a primary alcohol is mixed on cooling first with 0.5 mole of concentrated sulphuric acid and then with 1.25 moles of constantly boiling hydrobromic acid and the reaction mixture is heated to boiling. From secondary and tertiary alcohols there are prepared the corresponding alkyl bromides without addition of sulphuric acid to prevent the formation of olefins. (2) Equimolecular quantities of concentrated sulphuric acid and alcohol are mixed and the ethylsulphuric acid formed is heated with a small excess of potassium bromide. (3) The alcohol is treated with phosphorus tribromide or bromine is added to a mixture of red phosphorus and ethyl alcohol, which is gradually mixed.

Then from the bromide is prepared propionitrile (by the reaction with sodium cyanide in alcohol; see answer 93b). The nitrile is hydrolysed and the resulting propionic acid is brominated in the presence of red phosphorus (the Hell-Volhard-Zelinsky reaction). The thus synthesized bromoanhydride of 2-bromopropionic acid is treated with ethyl alcohol.

99. First, chloroacetic acid should be synthesized: calcium carbide $\rightarrow$ acetylene $\rightarrow$ acetaldehyde $\rightarrow$ acetic acid $\rightarrow$ chloroacetic acid.

An aqueous solution of acetic acid is then treated with dry soda; to the resulting solution of the sodium salt of chloroacetic acid is added a saturated solution of sodium nitrite and the reaction mixture is heated until no carbon dioxide is evolved.

100. (a) *n*-Propyl alcohol is dehydrated; the resulting propylene is converted to allyl alcohol (see answer 93a). The latter is treated with hydrogen bromide on irradiation with ultraviolet light.

(b) *n*-Propyl alcohol is first converted to propylene and then to allyl chloride (see answer 93a). The treatment of

the latter with chlorine water yields 1,3-dichloropropan-2-ol, which is subjected to hydrolysis to give glycerol.

(c) From *n*-propyl alcohol there is prepared allyl chloride (see answers 93a and 100b) which is treated with a solution of sodium iodide in acetone (see answer 93c). Allyliodide is a strong lachrymator.

101. (a) Ethyl alcohol is converted by dehydration to ethylene, which is introduced into chlorine water. The resulting ethylenechlorohydrin is treated with sodium cyanide in aqueous solution; the ethylenecyanohydrin formed is subjected to hydrolysis (see answers 93b and 95a and c).

(b) Ethylene is prepared from ethyl alcohol (see the previous answer). The passage of ethylene into bromine gives 1,2-dibromoethane (ethylene bromide).

Acetic acid is then synthesized by oxidation of ethyl alcohol and then potassium acetate is prepared from acetic acid by the action of potash. A mixture of potassium acetate and ethylene bromide is heated in glacial acetic acid to give ethylene glycol diacetate.

102. (a) Chloroacetic acid is first prepared from methyl alcohol (see answer 97) and then methyl ester by esterification. The methylchloroacetate thus synthesized is treated with sodium sulphide in methanol.

(b) Chloroacetic acid (for its synthesis from methanol see answer 97) is dissolved in water and treated with an excess amount of aqueous potassium hydrosulphide. The resulting thioglycolic acid is isolated as a barium salt, from which the free acid is obtained by the action of sulphuric acid.

103. (a) Chloroacetic acid (for synthesis of acetic and chloroacetic acids from methanol see answer 97) is converted on esterification to methyl ester. The treatment of the resulting methylchloroacetate with sodium methylate in excess absolute methanol gives methyl methoxyacetate. This ester is saponified with aqueous alkali and the reaction mixture is acidified to give methoxyacetic acid.

(b) Chloroacetic acid (see answers 97 and 103a) is converted to a sodium salt (by the action of soda). An aqueous solution of this salt is allowed to react with sodium acetate prepared from the original acetic acid (see answers 97 and 103a). The reaction mixture is carefully acidified with hydrochloric acid to give acetoxycetic acid.

(c) Acetic anhydride can be obtained by treating acetic acid (see answers 97 and 103a) with phosphorus pentoxide.

For this purpose use may also be made of another method which is usually employed for synthesis of mixed anhydrides, i.e., the interaction of the acid chloride with a salt of the corresponding acid.

104. The addition of hydrogen bromide to propylene yields isopropyl bromide, from which, by the action of sodium cyanide in an aprotic solvent (see answer 95a), there is synthesized first isobutyronitrile and then on hydrolysis (see answers 93b, 95a and c, and 101a) isobutyric acid itself. Dry distillation of the calcium salt of isobutyric acid gives diisopropyl ketone.

105. It should be taken into account that alkyl iodides cannot be made by direct iodination of alkanes. This is accounted for by the fact that hydrogen iodide (it must be evolved as a result of the substitution reaction) is a very strong reducing agent and is capable of converting the initially formed alkyl iodides into the corresponding hydrocarbons.

Three methods are most widely used to prepare alkyl iodides:

(a) The exchange reaction of alkyl chlorides or bromides with sodium iodide in acetone or methyl ethyl ketone. The resulting sodium chloride (or bromide) is insoluble in acetone and is therefore precipitated; owing to this circumstance the reaction goes to completion (the Finkelstein reaction; see also answer 93c). The yields of the corresponding alkyl iodides are as high as 80-95 per cent.

(b) The treatment of alcohols with phosphorus triiodide or a mixture of iodine and red phosphorus. With red phosphorus the reaction is carried out with addition of finely powdered iodine to a well stirred mixture of alcohol and red phosphorus (phosphorus triiodide is formed in the course of the reaction).

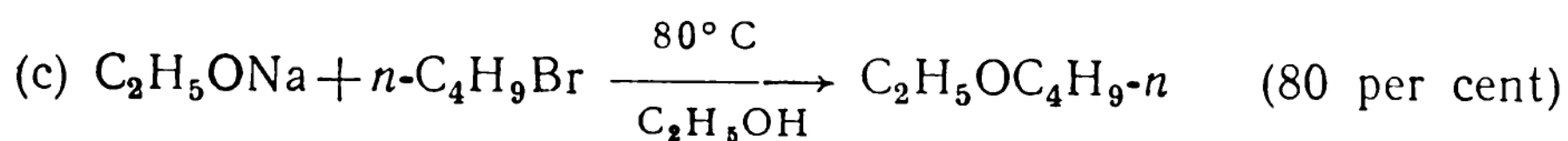
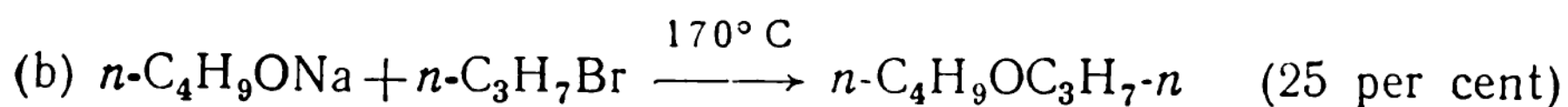
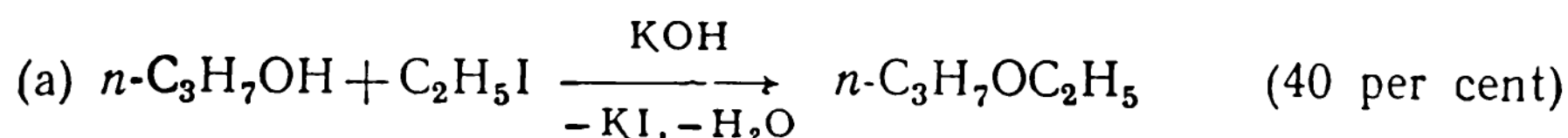
(c) The treatment of alcohol with sulphuryl chloride or chlorosulphonic acid yields the corresponding dialkyl sulphate. This compound is treated on heating with a saturated solution of sodium iodide (or potassium iodide).

Instead of dialkyl sulphates, use may be made of alkyl esters of *p*-toluenesulphonic acid (so-called tosylates), which

are easily obtained by treatment of the corresponding alcohols with *p*-toluenesulphochloride (tosyl chloride often designated as TosCl) in the presence of bases (pyridine).

106. In this case the course of the reaction is critically affected by the competition between the substitution and cleavage reactions (see W. H. Saunders, *Ionic Aliphatic Reactions*, Prentice-Hall, Englewood Cliffs, N. Y., 1965, page 77).

Ethers are made most smoothly from primary alkyl halides with unbranched radicals, but they cannot be obtained from tertiary alkyl halides by means of the methods indicated. The best results are secured by using the method "c". This can be borne out by the following examples:

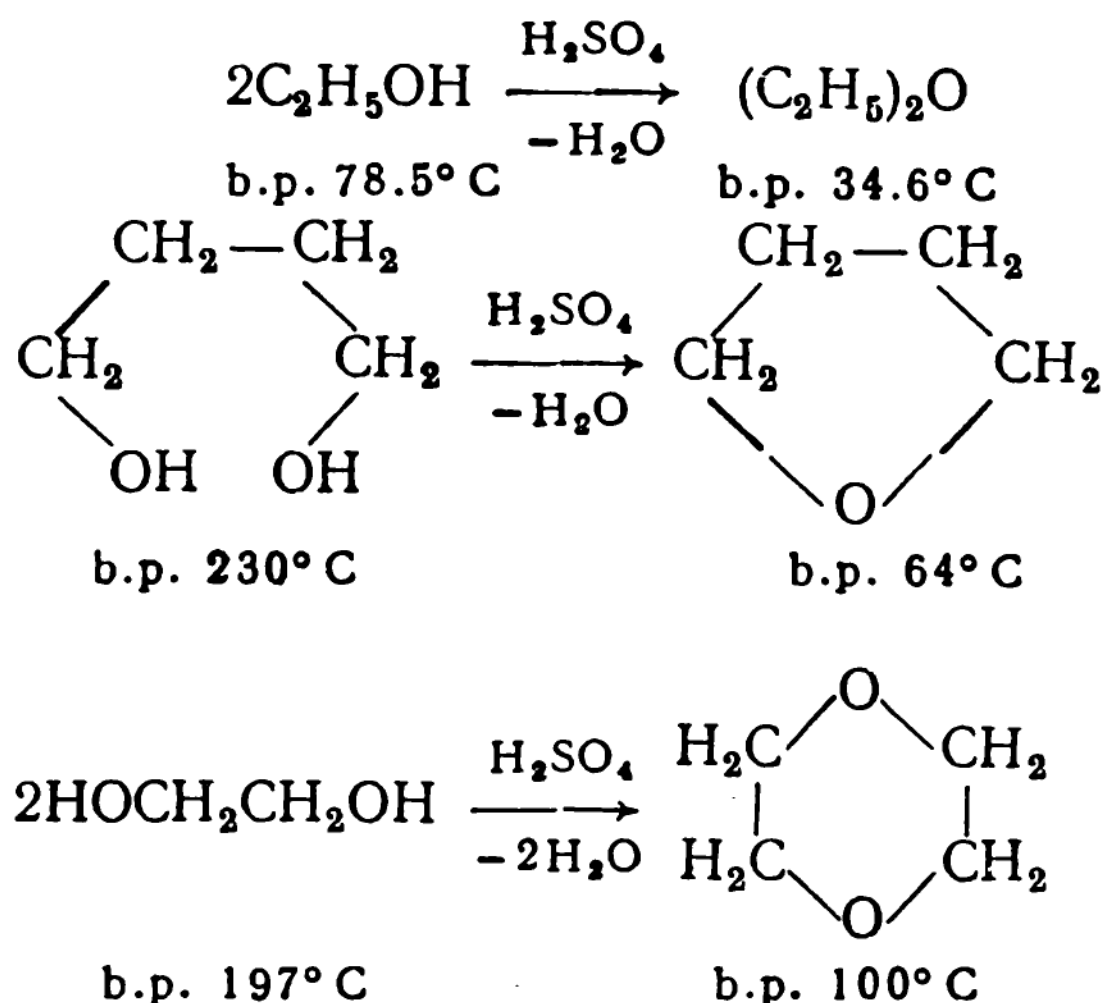


107. By using the action of sulphuric acid, ethers (symmetrical) are usually made from primary alcohols. This process is reversible since acidic reagents (including protic acids) split ethers (see the previous section). That is why use is made for this reaction of 0.2 mole of concentrated sulphuric acid per each mole of alcohol.

At the first step of the reaction there are formed alkylsulphuric acid and water at 100-130°C (it should be kept in mind that at temperatures over 170°C alkylsulphuric acids decompose to give the corresponding alkenes). Alkylsulphuric acid enters into the reaction with excess alcohol to form a symmetrical ether and sulphuric acid.

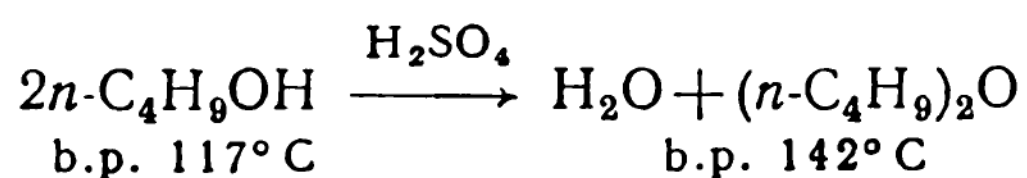
Ethers are unassociated and therefore often boil at a lower temperature than the starting alcohols. In this case, to avoid the occurrence of the reaction in the opposite direction, the ether is distilled off from the reaction mixture as it is formed.

Examples are syntheses of diethyl ether and also of cyclic ethers—tetrahydrofuran and dioxane:



If the boiling point of the ether obtained is higher than that of the starting alcohol (if the alkyl radical in the alcohol is sufficiently large), the water formed is removed from the reaction mixture. Ordinarily, a triple mixture consisting of water, alcohol and ether is distilled off, the distillate being dried and returned to the reaction vessel.

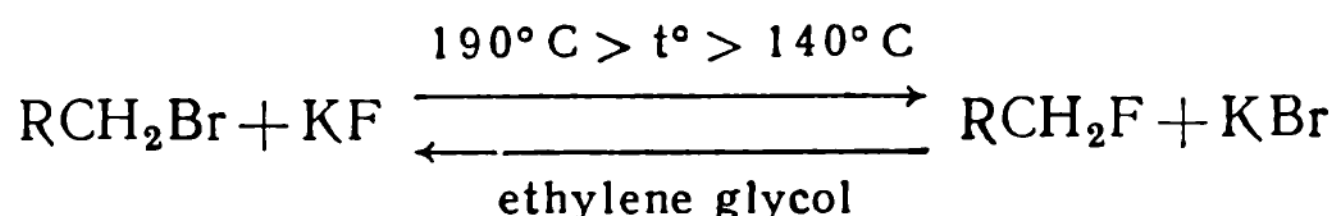
One example is the synthesis of di-*n*-butyl ether (an azeotropic mixture of water, alcohol and ether is distilled off at 91°C):



Asymmetrical aliphatic ethers are produced in satisfactory yields by using sulphuric acid provided that one of the alcohols is tertiary. The ethers formed are distilled off as an azeotropic mixture with water as they are formed. *tert* Butyl ethyl ether, for example, is prepared in 95 per cent yield by adding 1 mole of *tert*-butyl alcohol to the boiling mixture of 2 moles of ethanol and a 2.5-fold amount of 15-per cent sulphuric acid, the azeotropic mixture of ether and water being continually distilled off.

108. Primary alkyl fluorides are made by heating primary alkyl bromides with potassium fluoride in ethylene glycol (ethylene glycol dissolves organic and inorganic compo-

nents, thereby rendering the reaction mixture homogeneous). In this reaction an equilibrium is set up:



The boiling temperature of alkyl bromides is approximately 60°C higher than that of the corresponding fluorides. This circumstance is used to shift the equilibrium to the right, the alkyl fluorides being distilled off from the reaction mixture as they are formed. The reaction temperature must neither exceed the boiling point of ethylene glycol (197°C) nor be lower than 140°C because at lower temperatures no exchange reaction is expected to take place.

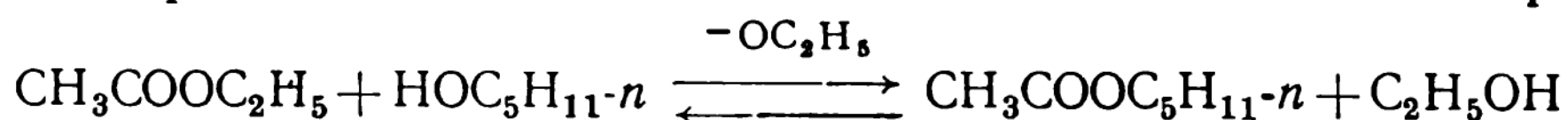
In view of this, the method described cannot be used for preparing alkyl fluorides $\text{C}_1\text{-C}_4$ since in this case the starting alkyl bromides boil at too low a temperature and, without having entered into the exchange reaction, are distilled off from the reaction mixture.

All primary *n*-alkyl fluorides of the composition $\text{C}_5\text{-C}_{16}$ have been prepared in this way.

109. (a) The nitrile of 2,3-dimethylbutan-1-oic acid; (b) methyl ether of 2-methylbutan-3-ol; (c) propionate of 2-methylbutan-3-ol; (d) 2-methylbut-2-ene.

110. (1) Esterification.

(2) Trans-esterification (an exchange reaction proceeding in the presence of traces of an alkoxide). For example,



For the equilibrium to be shifted in the desired direction use is made of a large excess of alcohol (*n*-amyl alcohol in this case).

- (3) The acylation of alcohols by acid anhydrides.
- (4) The acylation of alcohols by acid chlorides.
- (5) The interaction of acid chlorides with alkoxides.
- (6) The interaction of acid salts with alkyl halides.
- (7) The alkylation of salts of carboxylic acids by dialkyl sulphates.
- (8) The alkylation of carboxylic acids by diazomethane.
- (9) The alcoholysis of nitriles (see answer 98).
- (10) The acylation of alcohols by ketenes.

111. First, propylene is hydrated to give isopropyl alcohol. Then propionic acid is synthesized by addition of hydrogen bromide to propylene contrary to the Markovnikov rule (see answers 93b, 96, 100a); the resulting bromide is hydrolysed to *n*-propyl alcohol, which is subjected to oxidation. The isopropyl alcohol is acylated by propionyl chloride prepared from propionic acid.

112. Isopropyl alcohol is converted by dehydration first to propylene and then to isobutyric acid (see answer 104). The treatment of isopropyl alcohol with isobutyric acid chloride in the presence of dry pyridine gives rise to isopropylisobutyrate.

113. (a) Ethyl alcohol is used to prepare ethyl bromide (by the action of hydrogen bromide, red phosphorus and bromine, phosphorus tribromide or, finally, by successive treatment with concentrated sulphuric acid and potassium bromide) or diethyl sulphate (by the action of sulphuryl chloride). One of these reagents is used to alkylate sodium phenolate.

(b) 1,2-Dibromoethane is prepared from ethyl alcohol (see answer 101b) and is treated with a solution of sodium phenolate in ethyl alcohol.

(c) From ethyl alcohol there is made a sodium salt of chloroacetic acid (see answer 103b), which is treated with a solution of phenol in aqueous alkali and the reaction mixture is then acidified.

114. Benzyl chloride produced from toluene by a free-radical chlorination is heated in aqueous-alcoholic solution with potassium cyanide to synthesize benzyl cyanide (phenylacetone nitrile). The hydrolysis of benzyl cyanide gives rise to phenylacetic acid and when it is subjected to alcoholysis (see answer 98), an ester of the acid results.

115. The free-radical chlorination of toluene can yield the following products of different degrees of substitution, depending on the reaction time and the amount of chlorine introduced into the reaction: benzyl chloride, benzylidene chloride, and benzotrichloride. These chlorides are hydrolysed to give benzyl alcohol, benzaldehyde, and benzoic acid, respectively.

(a) Hydrolysis of benzyl chloride is carried out with an aqueous solution of potash.

(b) Benzylidene chloride is hydrolysed by heating with water in the presence of calcium carbonate or powdered iron (to bind the hydrogen chloride evolved).

(c) Benzotrichloride is hydrolysed to benzoyl chloride by using a calculated amount of water in the presence of concentrated sulphuric acid (an industrial method of synthesis). Benzoyl chloride can be hydrolysed to benzoic acid by using an excess amount of water in the presence of acid or alkali (with alkali the reaction mixture must be acidified).

(d) To an aqueous solution of hydrogen peroxide are added alternately a solution of sodium hydroxide and benzoyl chloride (see answer 115c).

116. (a) To prepare anisole, a solution of phenol in 2*N* sodium hydroxide is treated with dimethyl sulphate (which can be prepared by treatment of methyl alcohol with sulphuryl chloride or chlorosulphonic acid).

(b) From methyl alcohol there is obtained chloroacetic acid (see answer 97), which is converted first to phenoxyacetic acid (see answer 113c) and then, by esterification, to its methyl ester.

(c) First, phenoxyacetic acid is prepared from methyl alcohol (see answer 116b) and then its sodium salt is obtained by treating the acid with soda. Besides, methyl alcohol is also used to synthesize acetic acid (see answer 97), from which acetyl chloride is then made. Mixing of equimolecular amounts of both reagents (the salt must be dry) yields a mixed anhydride.

(d) Phenol enters into an esterification reaction with difficulty. Phenyl acetate can be synthesized by the action of an equimolecular amount of acetyl chloride or acetic anhydride on phenol in the presence of small quantities of phosphoric or sulphuric acid as a catalyst.

117. The free-radical bromination of methyl benzenes proceeds smoothly until the corresponding monobromomethyl derivatives are formed and somewhat less easily up to the formation of dibromomethyl derivatives. Tribromomethyl compounds cannot yet be made in this way. The complete free-radical bromination of *o*-xylene yields the corresponding tetrabromide. To prepare *o*-phthalic aldehyde from it, the hydrolysis is best accomplished in aqueous-alcoholic solution in the presence of potassium oxalate.

118. (a) Phenylacetic acid is synthesized from toluene (see answer 114); dry distillation of its calcium or iron salt yields dibenzyl ketone.

(b) The free-radical chlorination and subsequent hydrolysis of toluene gives benzyl alcohol (see answer 115a) and benzoyl chloride (see answer 115c). The reagents are shaken with a 2*N* solution of alkali (the Schotten-Baumann reaction).

119. (a) *N,N*-Diethylallylamine can be made by heating a mixture of allyl chloride with a threefold or fourfold excess of diethylamine in the presence of dry potash.

N,N-Diethylbenzylamine is prepared from benzyl chloride in an analogous way. The yield in both cases is about 80 per cent.

(b) and (c) When ethylene oxide is allowed to react with a large excess of ammonia, monoethanolamine is predominantly formed on cooling. If an excess of ethylene oxide is used and the reaction mixture is not cooled, triethanolamine is exclusively formed.

120. Ethanol is converted to ethylene (see answers 101a and b) and then to ethylene chlorohydrin (see answer 101a). The latter is used for synthesis of triethanolamine; this can be achieved in two ways:

(1) By treatment of a solution of ammonia with excess ethylene chlorohydrin in the presence of potash and water.

(2) By conversion of ethylene chlorohydrin into ethylene oxide.¹

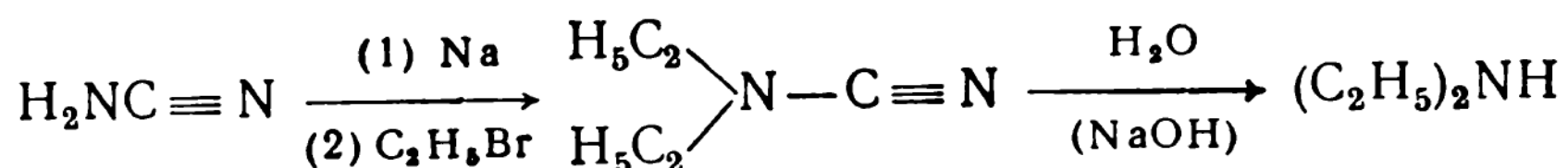
The triethanolamine thus obtained is allowed to react with thionyl chloride to give β,β',β'' -trichlorotriethylamine.

121. Ethanol is converted into ethylene chlorohydrin (see answer 101a) from which ethylene oxide (see answer 120) and monoethanolamine (see answer 119b) are prepared. Monoethanolamine is first converted by the action of 48-per cent hydrobromic acid to β -bromoethylamine hydrobromide and then, by treatment with soda, to a free base, which on interaction with sodium (or potassium) hydrosulphide is converted to β -mercaptoethylamine.

122. Cyanamide is successively treated with metallic sodium, ethyl bromide (prepared from ethanol as in answer

¹ Ethylene oxide is produced commercially by direct oxidation of ethylene in the presence of catalysts.

98b) and alkali to give diethylamine:



Diethylamine is then alkylated by the ethylene chlorohydrin prepared from ethanol (see answers 101a and 120). The thus obtained β -N,N-diethylaminoethanol is treated first with 48-per cent hydrobromic acid (see answer 121) and then with an excess of an alcoholic solution of ammonia at room temperature to give N,N-diethylethylene diamine.

123. From ethanol there is first prepared chloroacetic acid (see answer 98a) and then, by treatment with an excess amount of a soda solution, an alkaline solution of its sodium salt.

Dibromoethane is also simultaneously prepared from ethanol (see answer 101b); it is converted by heating in a closed vessel with a 20-fold excess of 25-per cent ammonia in the presence of small amounts of copper sulphate into ethylenediamine hydrobromide and then to a free base.

The interaction of aqueous solutions of both reagents gives the sodium salt of N,N,N',N'-ethylenediaminetetraacetic acid.

When the reaction mixture is acidified, N,N,N',N'-ethylenediaminetetraacetic acid, which is poorly soluble in water, precipitates.

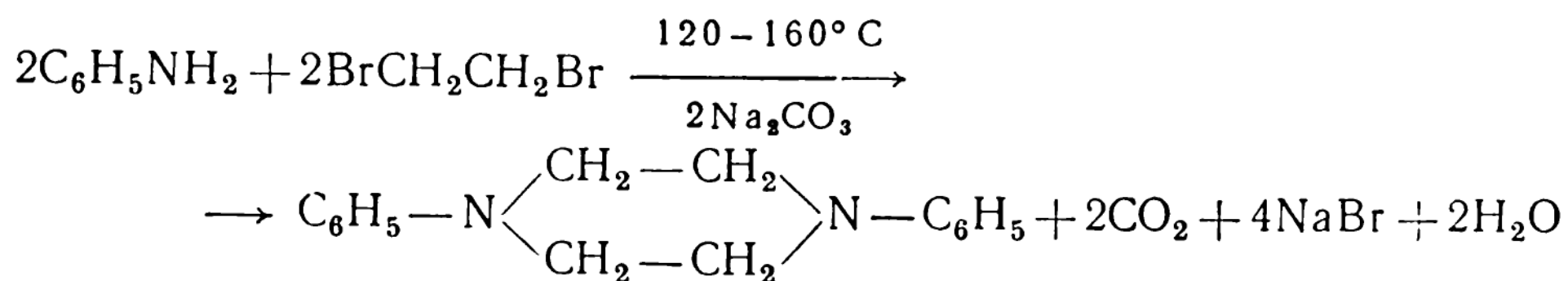
124. The synthesis of amines, by means of the Hofmann reaction, from alkyl halides and ammonia usually gives a mixture of primary, secondary and tertiary amines and the salt of the corresponding quaternary ammonium base. The product ratio depends on the molar ratio of the reagents and the reaction conditions.

Mixtures of amines are most easily separated when the components strongly differ in molecular weight and hence in boiling temperature. This happens when the radical in the starting alkyl halide, which replaces hydrogen in ammonia, is sufficiently large. It is for this reason that distillation, which is the most time-consuming method of separating a mixture of primary, secondary and tertiary amines (the salt of quaternary ammonium base, like any other ionic compound, is not distilled), is applicable for complete se-

paration of mono-, di-, and tri-*n*-hexylamines, but it is much less effective if a mixture of ethylamines is involved.

125. Use is made of the Gabriel synthesis.

126. (a) First ethylene bromide is prepared from ethanol (see answer 101b). Then equimolecular quantities of ethylene bromide, aniline, and soda are mixed and heated to 120-160°C:



(b) First ethylene chlorohydrin is prepared from ethanol (see answer 101a) and one mole of it is heated with 2 moles of aniline. The reaction mixture is neutralized with sodium hydroxide and excess aniline is distilled off together with steam.

Monoethanolaniline can also be made from ethylene oxide and aniline.

127. First ethyl bromide is made from ethanol (see answer 98b) and then diethylamine (see answer 122).

Then ethylbenzene is chlorinated at the side chain (see Chapter II) and the resulting chloride is treated with alcoholic alkali. The styrene thus obtained is converted by the action of chlorine water into chlorohydrin and then, by the action of alkali, into styrene oxide. The interaction of diethylamine with styrene oxide gives 2-diethylamino-1-phenylethan-1-ol.

128. The chlorination of propylene yields allyl chloride (see Chapter II), which is then converted to allyl cyanide (for preparation see answers 93b, 95a and c, and 101a). To the last-named compound is added hydrogen bromide contrary to the Markovnikov rule. The nitrile obtained is introduced into the Gabriel reaction. The acid hydrolysis or treatment of a phthalimide derivative with hydrazine hydrate gives γ -aminobutyric acid.

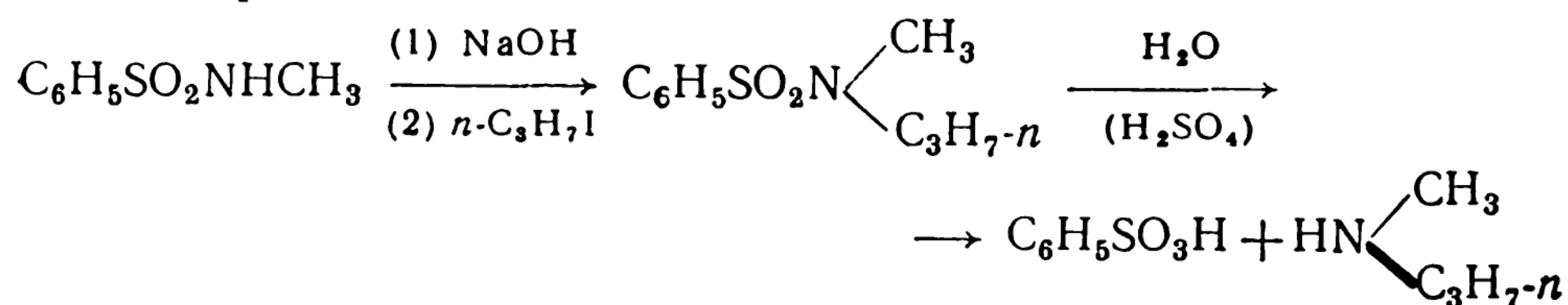
129. (a) When dry hydrogen chloride is passed into boiling tetrahydrofuran, 4-chlorobutan-1-ol results. The treatment of this compound with potassium phthalimide and then with hydrazine hydrate in ethanol (on heating) results in the formation of 4-aminobutan-1-ol.

(b) When tetrahydrofuran is boiled with a mixture of potassium iodide and phosphoric acid, 1,4-diiodobutane is formed. The successive treatment of the resulting compound with potassium phthalimide and hydrazine hydrate (see answers 128 and 129a) yields 1,4-diaminobutane (tetramethylene diamine).

130. (1) The passage of a mixture of a primary amine and alcohol over aluminium oxide heated up to about 300°C.

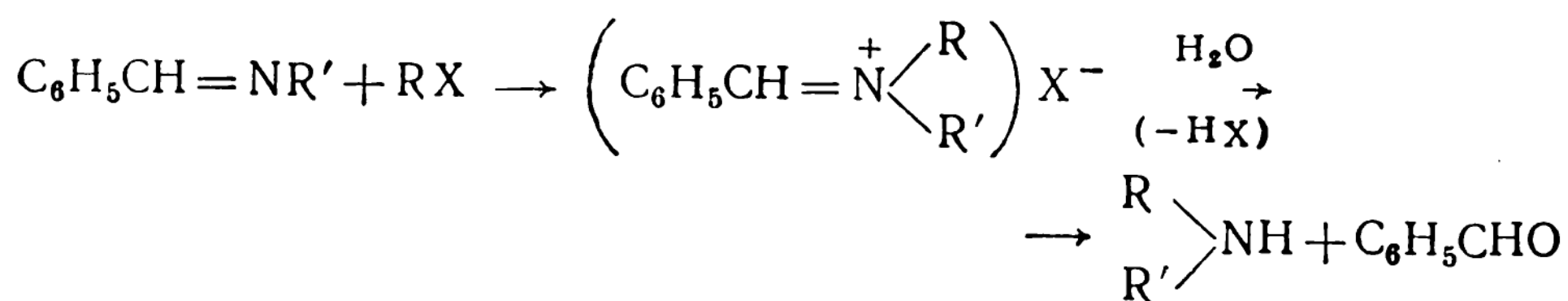
Depending on the ratio of the reagents and the time of contact with the catalyst, secondary and tertiary amines can be prepared in various proportions¹. At sufficiently large R' (see answer 124) they can be easily separated by distillation.

(2) To synthesize secondary amines with different alkyl radicals use may also be made of the reaction of alkyl halides with potassium or sodium derivatives of alkylsulphamides, for example,



The benzenesulphonic acid formed is removed on treatment with alkali.

(3) Use may also be made for this purpose of azomethins (Schiff bases):



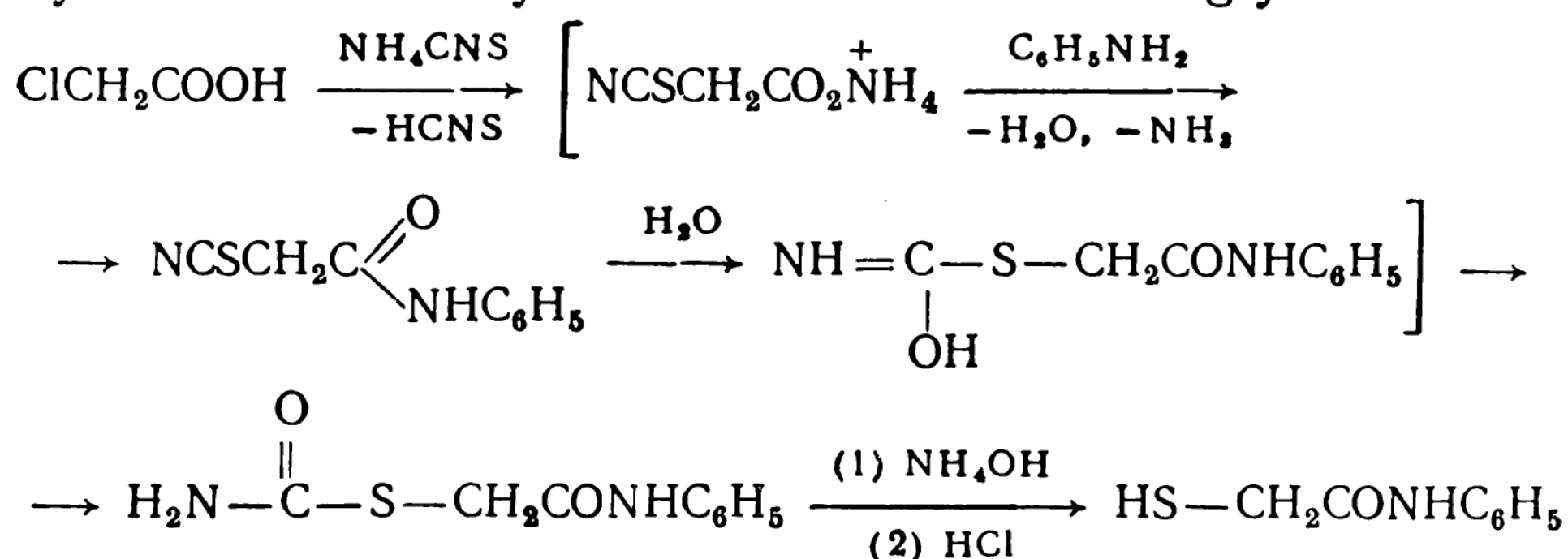
The amine can be isolated from the reaction mixture as a water-soluble salt (for example, as hydrochloride).

131. α -Bromobutyric acid bromide is synthesized from *n*-propanol in just the same way as α -bromopropionic acid bromide from ethanol (see answer 98b). Then the acid bromide is hydrolysed to give α -bromobutyric acid; the amination of the latter with an aqueous solution of ammonia in the

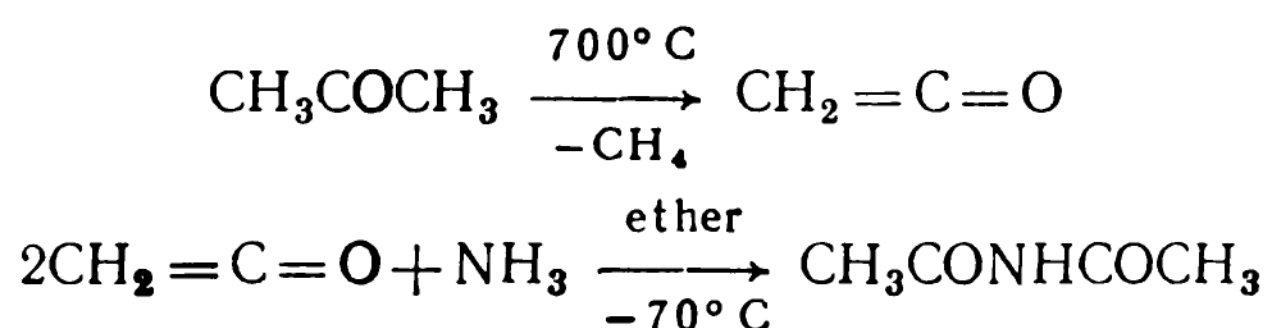
¹ No quaternary ammonium bases are formed in this reaction.

presence of ammonium carbonate yields α -aminobutyric acid.

132. The free-radical chlorination of acetic acid gives chloroacetic acid (see answers 97, 98a, etc.). The latter is treated with excess of ammonium rhodanide and then the resulting ammonium salt of thiocynoacetic acid is heated with aniline in absolute alcohol. The hydrolysis of the reaction product with an aqueous solution of ammonia and subsequent acidification of the reaction mixture with dilute hydrochloric acid yields the anilide of thioglycolic acid:



133. The dry distillation of the calcium salt of acetic acid gives acetone. When the latter is subjected to pyrolysis on a nichrome filament heated to 700°C (this device is known as the "ketene lamp"), ketene is formed (Poison!). Ethereal solutions of ketene (2 moles) and ammonia are mixed and after the ether is distilled off, N-acetylacetamide results:



134. The treatment of optically active butan-2-ol with *p*-toluenesulphonic acid chloride in the presence of pyridine yields the corresponding ester (tosylate). The asymmetric centre remains intact in this case and hence the configuration and optical activity are retained. When the tosylate formed is treated with a solution of ammonia in dimethylformamide, there takes place a substitution reaction by the $\text{S}_{\text{N}}2$ mechanism, the configuration is inversed, but the resulting 2-aminobutane remains optically active (for more detail

see W. Saunders, *Ionic Aliphatic Reactions*, Prentice-Hall, Englewood Cliffs, N. Y., 1965, page 35.

135. Mono- and di-N-alkylation of aniline can be carried out with the corresponding alcohols in the presence of sulphuric acid.

If however it is necessary to prepare only monoalkylaniline, it is recommended that sulphuric acid be replaced with Raney nickel. The boiling of aliphatic alcohols of the composition C_2-C_6 with aniline in the presence of the nickel catalyst enables preparation of monoalkylanilines in yields of the order of 60 per cent.

The method described above can be used to produce N-ethylaniline from ethanol and aniline.

When N-ethylaniline is heated with ethylene chlorohydrin (for preparation from ethanol see answer 101a) in the presence of soda, N-ethyl-N- β -hydroxyethylaniline results.

136. (1) The alkylation of ammonia with *n*-propyl halides (see answer 124).

(2) The alkylation of ammonia with *n*-propyl alcohol: *n*-propyl alcohol and a current of ammonia are passed over aluminium oxide heated to about 300°C. The resulting mixture of primary, secondary and tertiary amines is separated into its components by distillation (see answers 124 and 130).

(3) The alkylation of ammonia by di-*n*-propyl sulphate.

(4) The action of sodium amide on *n*-propyl bromide in liquid ammonia at -70°C . It should be kept in mind that at higher temperatures there takes place an elimination of hydrogen halide and the corresponding olefins are formed (propylene in the case indicated above).

(5) The synthesis of *n*-propylamine can also be accomplished by the Gabriel procedure from *n*-propyl halide and potassium phthalimide (see answer 129, a and b).

(6) The Hofmann rearrangement of the amide of *n*-butyric acid.

(7) The Curtius rearrangement of the azide of *n*-butyric acid.

(8) The Beckmann rearrangement of the oxime of di-*n*-propyl ketone (butyrone) and the hydrolysis of the resulting N-propyl amide of butyric acid.

137. (a) 2-Aminobutane. (b) Benzylamine.

138. (a) Methyl ethyl ketone. (b) Acetaldehyde.

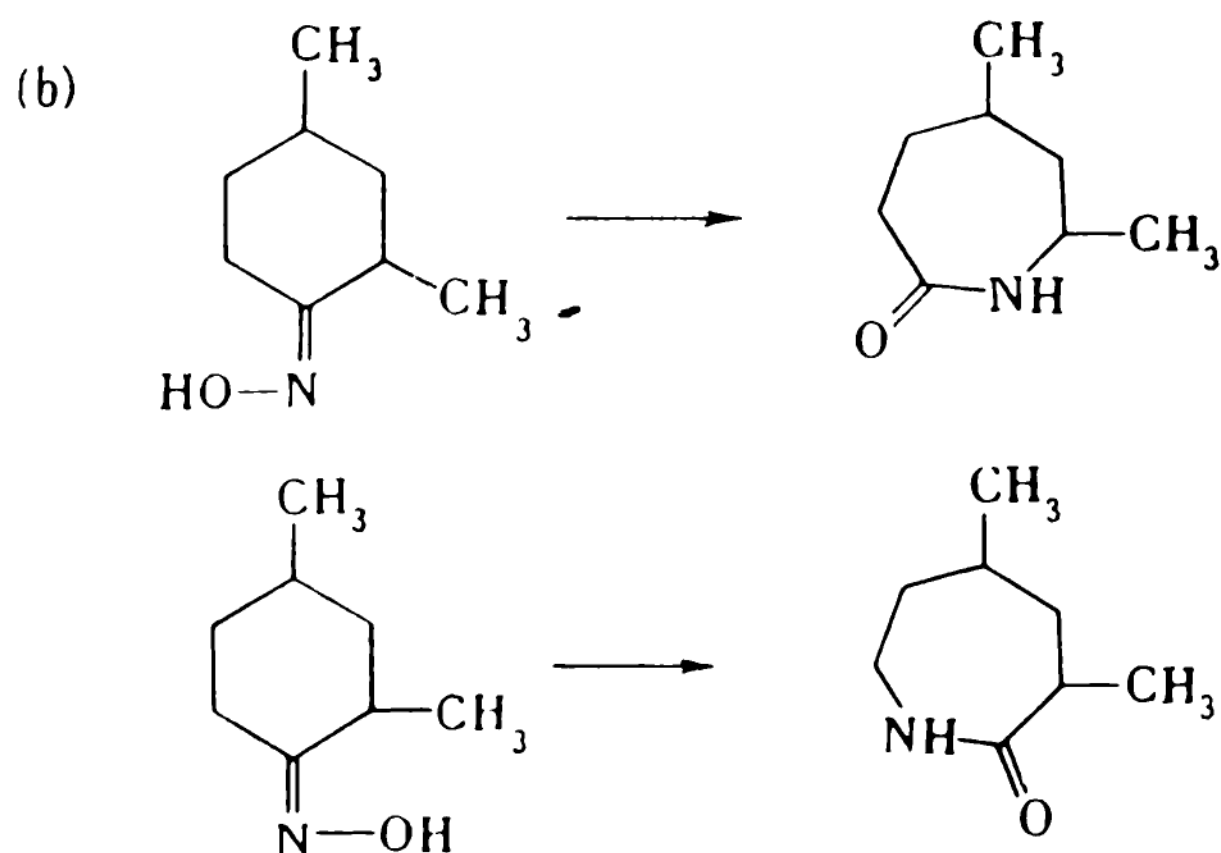
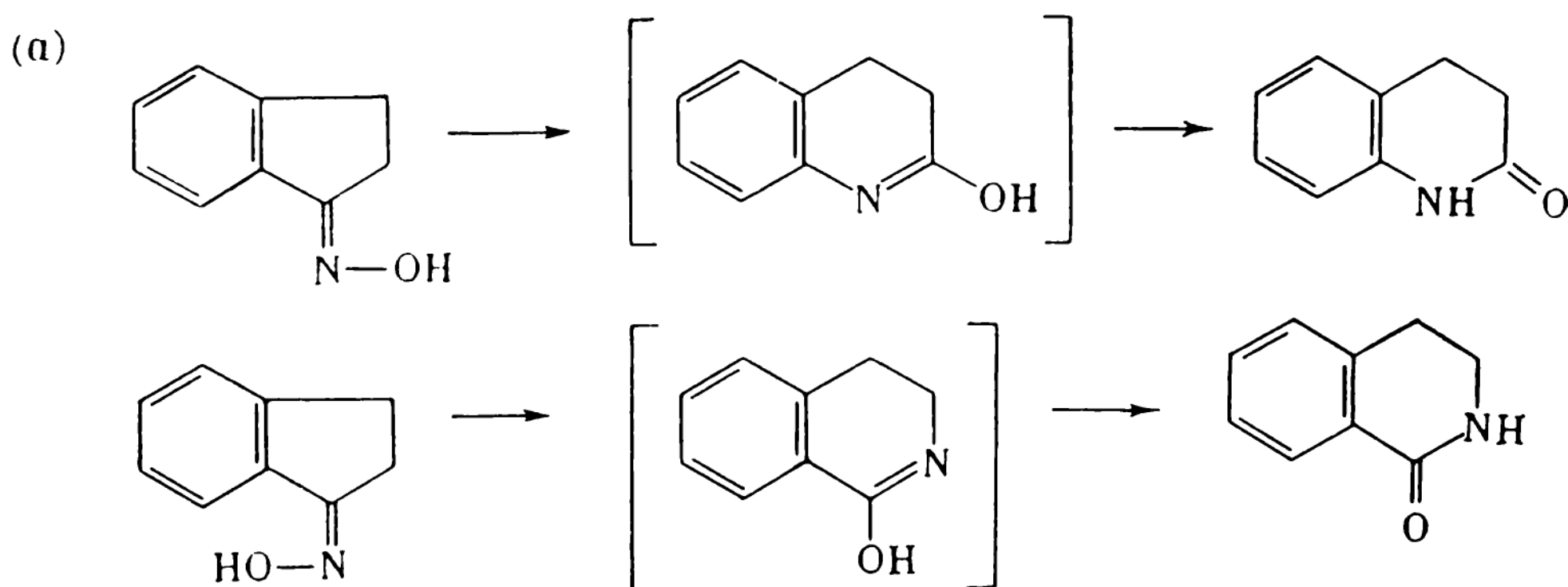
139. Succinic acid is converted by heating with ammonium carbonate into succinimide, which is then subjected to the Hofmann rearrangement to form β -alanine (β -aminopropionic acid).

140. The methyl isocyanate formed reacts with acetamide that has not yet entered into the reaction (concerning the mechanism of the Hofmann reaction see A. R. Surrey, *Name Reactions in Organic Chemistry*, Academic Press, New York and London, 1961, page 134).

141. From the oxime of cyclopentanone there is derived the lactam of δ -aminovaleric acid, and from the oxime of cyclohexanone, the lactam of ϵ -aminocaproic acid (caprolactam).

142. An oxime is derived from benzophenone and subjected to the Beckmann rearrangement and the resulting anilide of benzoic acid is hydrolysed.

143.



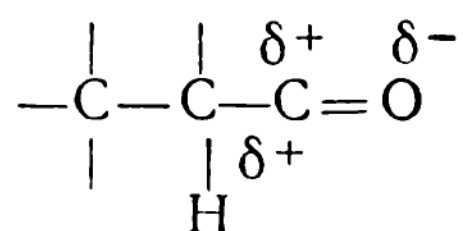
CHAPTER 4

CONDENSATION REACTIONS AND TAUTOMERISM OF CARBONYL COMPOUNDS

INTRODUCTION

Carbonyl compounds which imply in the narrow sense aldehydes and ketones and, in a broader sense, also acids and their derivatives, constitute one of the most reactive classes of organic compounds. The various transformations characteristic of these compounds, the formal difference between the reactions in which they take part, the specificity conferred on the reactivity of these compounds by tautomeric transformations, all these features create certain difficulties in studying this section of organic chemistry by students. In order to cope with these difficulties it is important to find the common features in the many externally dissimilar transformations.

The reactivity of carbonyl compounds is associated with the three reaction centres contained in them:



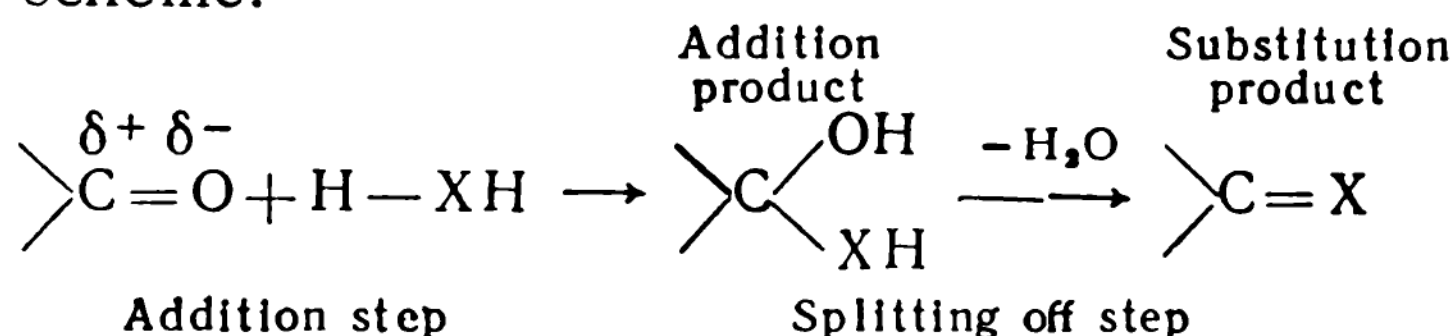
The first centre is the carbonyl carbon atom bearing a partial positive charge and therefore capable of reacting with nucleophilic reagents, say, with the alcoholate anion, the cyanide anion, the free electron pair of the nitrogen of ammonia, amines and of many other compounds of trivalent nitrogen.

The second centre is the negatively charged oxygen capable of interacting with electrophilic reagents and, primarily, of accepting a proton. This proton addition increases the positive charge on the carbonyl carbon atom, thereby favouring the occurrence of the reaction across this centre (acid catalysis).

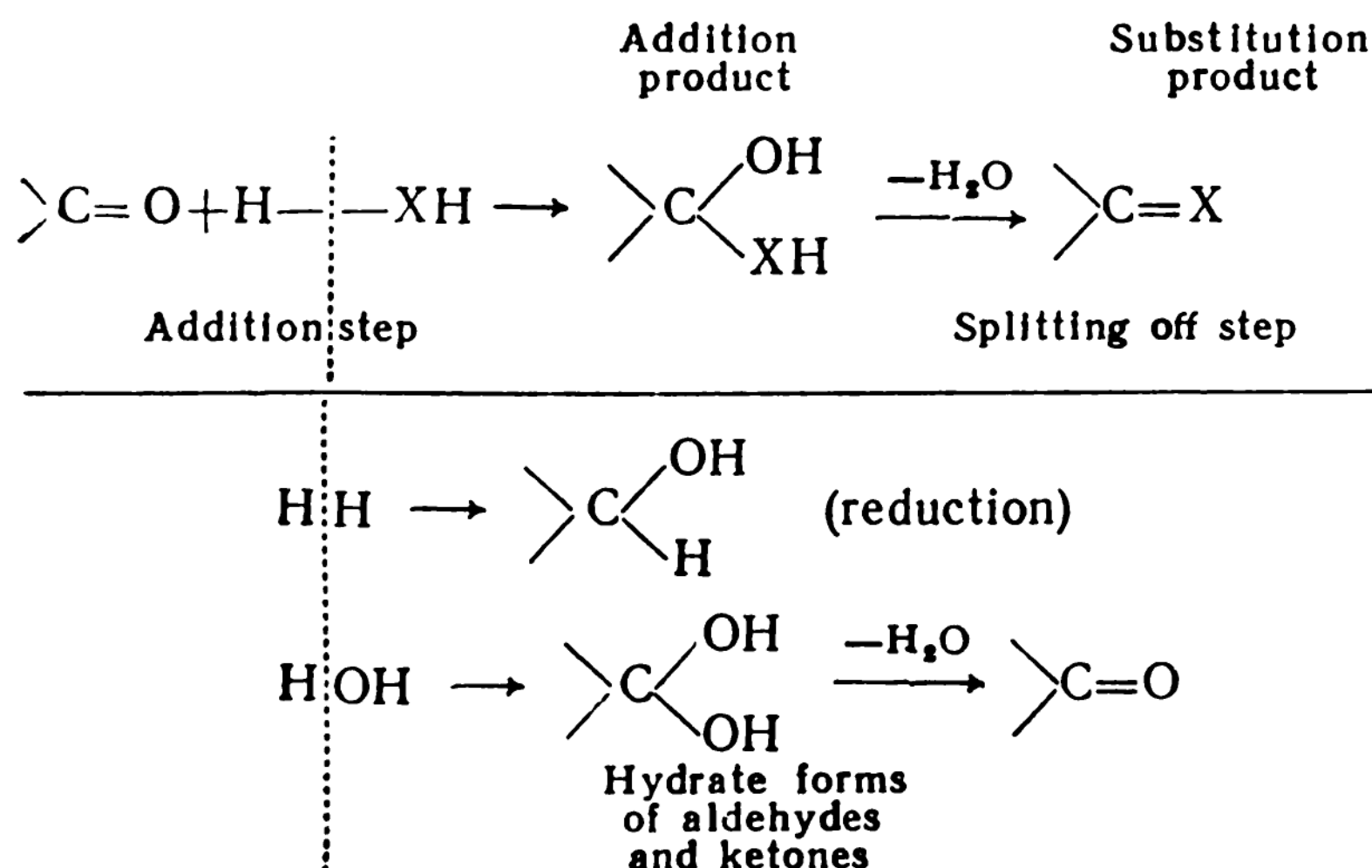
The third centre is made up of "mobile" hydrogen atoms situated in the α -position to the carbonyl group. Under the influence of the adjacent carbonyl group they are capable of splitting off as a proton by the action of bases. The remaining part of the molecule of the carbonyl compound acquires the anionic character and can itself function as a nucleophilic reagent.

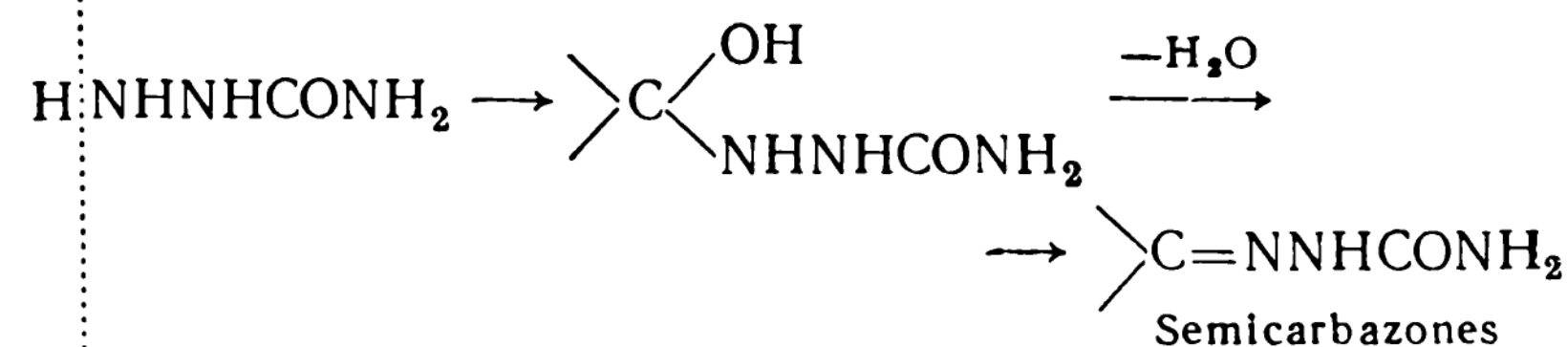
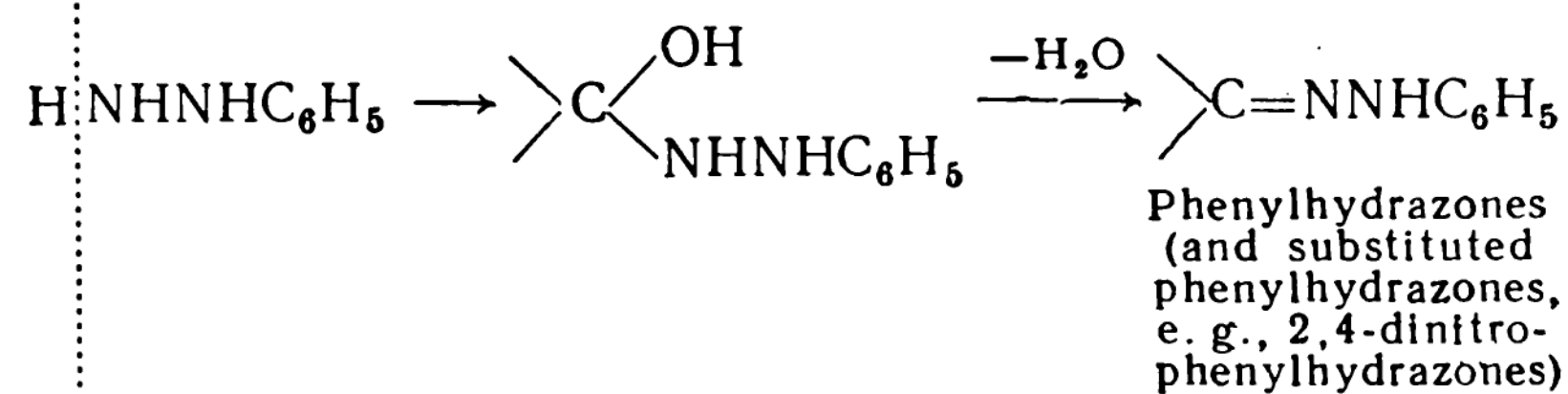
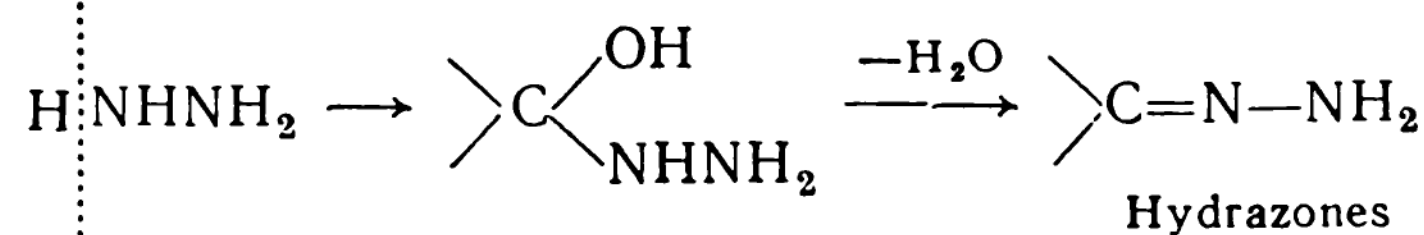
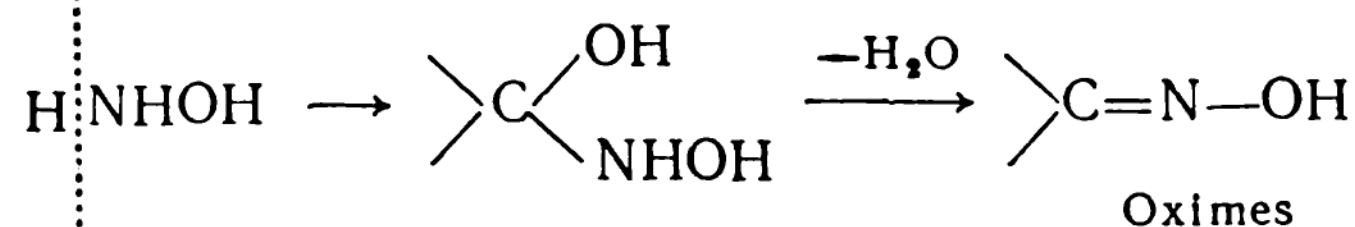
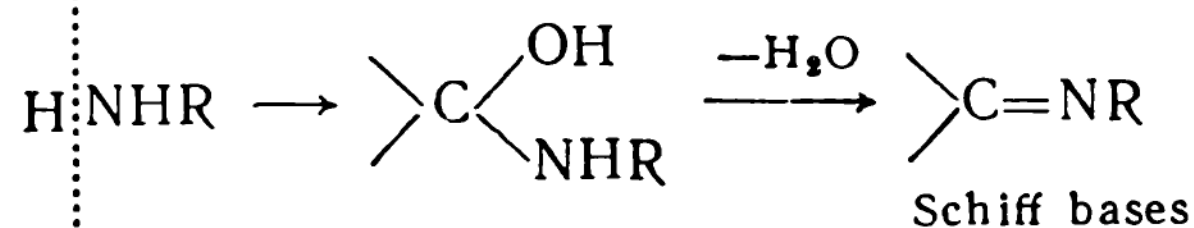
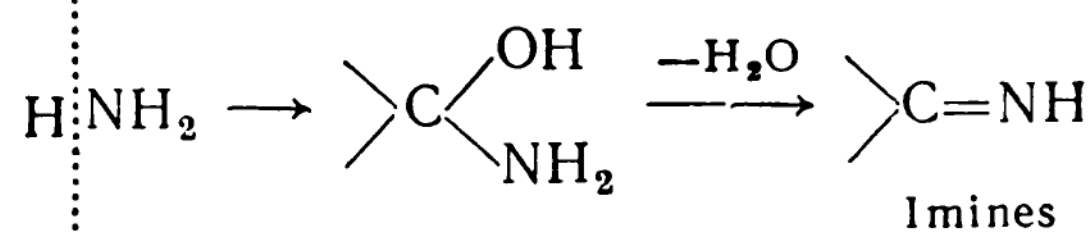
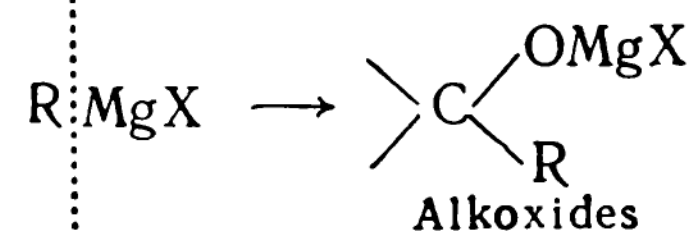
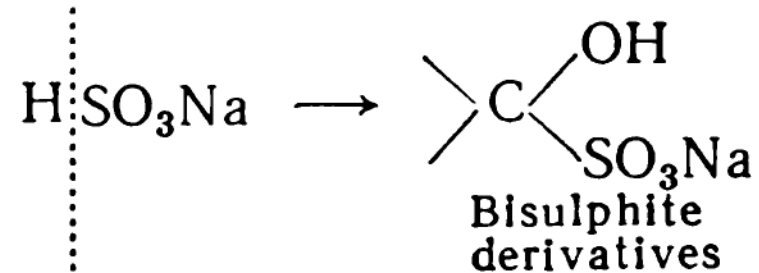
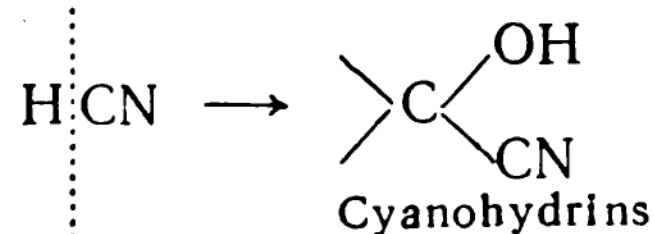
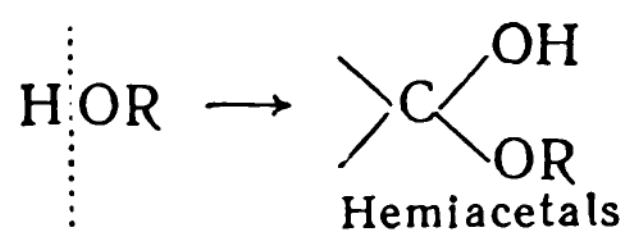
These three possibilities should always be "tied up" to the case being considered.

The reactions of carbonyl compounds proper (aldehydes and ketones) are known to be classified into addition and substitution reactions. For convenience, this classification may be dispensed with and it may be assumed that substitution reactions constitute the subsequent step of addition reactions, i.e., both types of reaction can be represented by a single scheme:



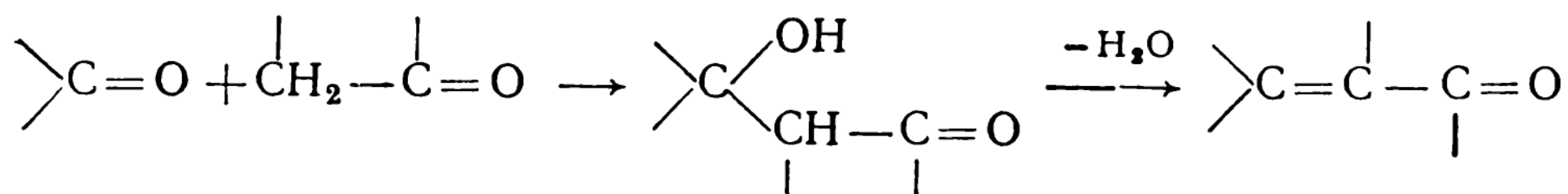
This approach is the more justified that some reactions of substitution involve the formation of intermediate addition products, while such products in other reactions seem at least probable. Below are listed the reactions of aldehydes and ketones that correspond to the general scheme given above:



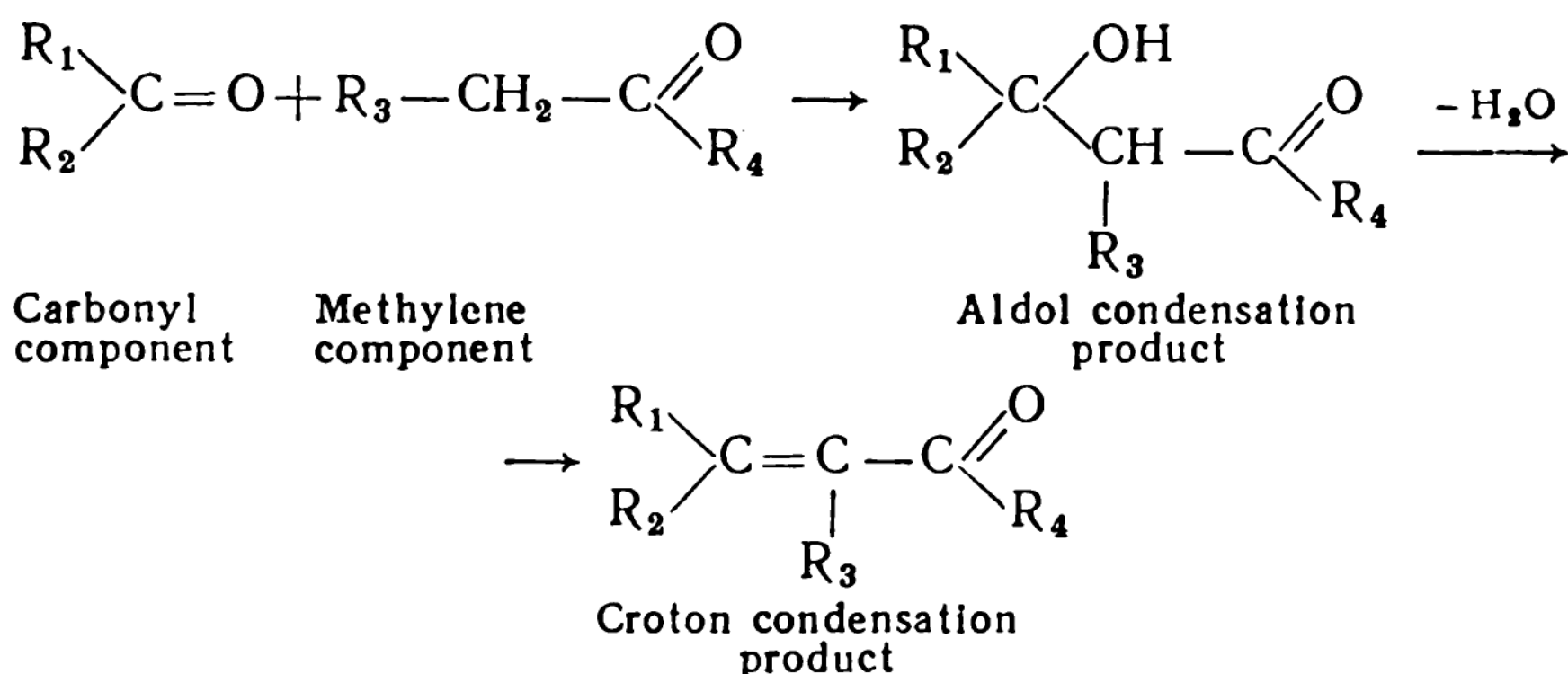


Considering the table given above, one can easily be convinced that substitution reactions are induced by the interaction of aldehydes and ketones with ammonia derivatives of the general formula $\text{H}_2\text{N}-\text{R}$.

The same table formally includes also an aldol-croton condensation:



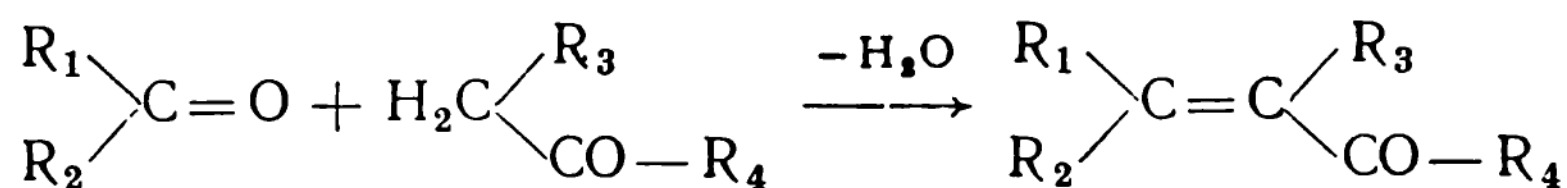
Condensation reactions however are more conveniently generalized in the form of the following table:



Carbonyl component ¹			Methylene component ¹			Product of aldol condensation	Product of croton condensation
R ₁	R ₂	name	R ₃	R ₄	name		
CH ₃	H	Acetaldehyde	H	H	Acetaldehyde	Aldol	Crotonaldehyde
R	H	Aldehydes	R	H	Aldehydes	Aldol homologues	Homologues of crotonaldehyde
CH ₃	CH ₃	Acetone	H	CH ₃	Acetone	Diacetone alcohol	Mesityl oxide
R	R	Ketones	R	R	Ketones	Homologues of diacetone alcohol	Homologues of mesityl oxide
H	H	Formaldehyde	CH ₃	CH ₃	Acetone	Oxymethylene acetone	Methyl vinyl ketone

¹ R is the hydrocarbon radical

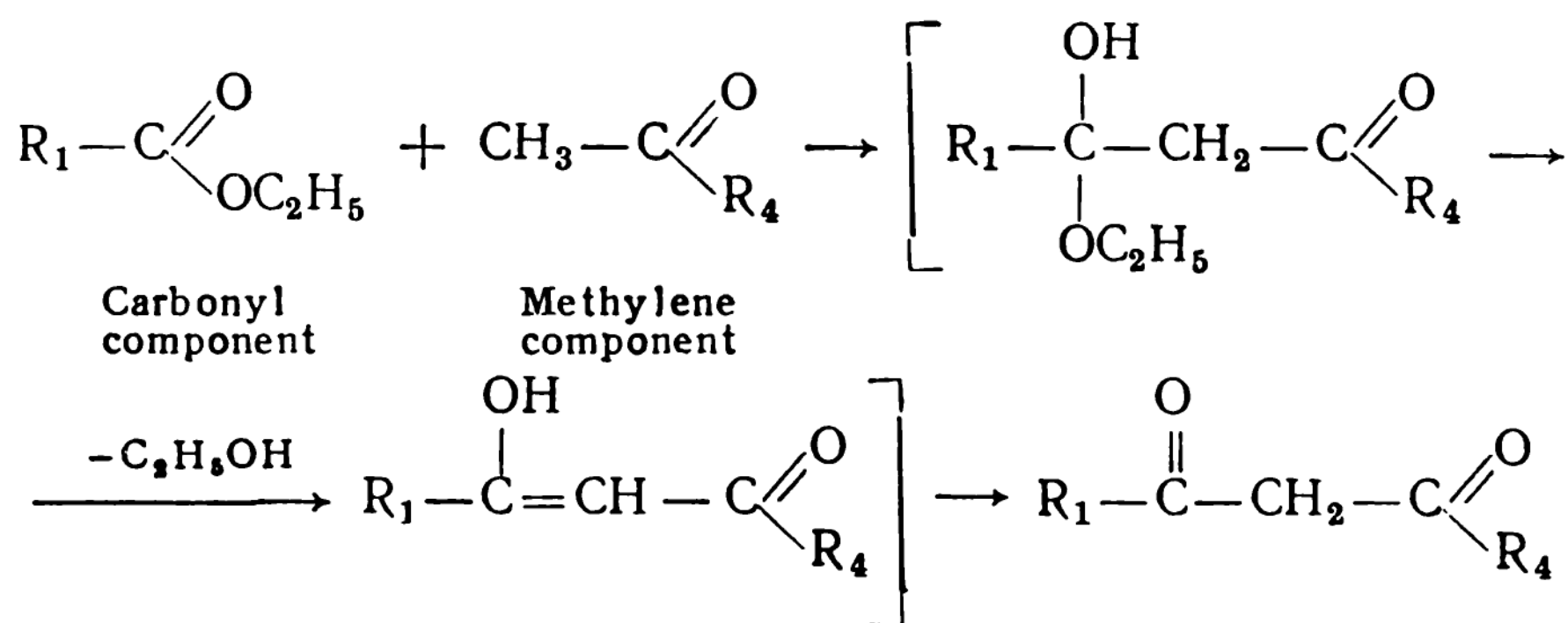
This scheme also includes condensations of the Perkin reaction type which differ from those given above in that the role of the methylene component is played by carboxylic acids or their functional derivatives (ester, anhydride) and the corresponding unsaturated compounds are formed (a condensation resembling the croton condensation):



Carbonyl component			Methylene component			Condensation product
R ₁	R ₂	name	R ₃	R ₄	name	
C ₆ H ₅	H	Benzaldehyde	H	OC ₂ H ₅	Ethylacetate	Ethyl cinnamate
CH ₃	CH ₃	Acetone	COOH	OH	Malonic acid	Dimethylacrylic acid ¹
C ₆ H ₅	H	Benzaldehyde	H	OCOCH ₃	Acetic anhydride	Cinnamic acid
C ₆ H ₅ CH=CH	H	Cinnamic aldehyde	C ₆ H ₅	OH	Phenylacetic acid	1,4-Diphenylbuta-1,3-diene ¹

¹ After decarboxylation

One can compare the aldol-croton condensation of aldehydes and ketones with ester condensations by assuming the latter to proceed according to the same scheme but with splitting off (at the "croton" stage) of an alcohol instead of water and ketonization of the enol formed:



The role of the methylene component can be performed here not only by esters but also by aldehydes and ketones.

Carbonyl component		Methylene component		Condensation product
R ₁	name	R ₂	name	
CH ₃ H C ₆ H ₅	Ethyl acetate Ethyl formate Ethyl benzoate	OC ₂ H ₅ OC ₂ H ₅ OC ₂ H ₅	Ethyl acetate Ethyl acetate Ethyl acetate	Acetoacetic ester Formylacetic ester Benzoylacetic ester
CH ₃ H CH ₃	Ethyl acetate Ethyl formate Ethyl acetate	CH ₃ CH ₃ C ₆ H ₅	Acetone Acetone Acetophenone	Acetylacetone Formylacetone Benzoylacetone

It must be emphasized that the formal similarity between the reactions given above should not be taken as the actual agreement between their mechanisms. This comparison has been made primarily in order to facilitate the remembering of the results of numerous reactions and not to disclose all the details of their true mechanism.

Problems and Exercises

1. GENERAL PROPERTIES OF CARBONYL COMPOUNDS. TAUTOMERISM

1. What types of organic compounds are referred to as carbonyl compounds (in the broad sense of the term)?

2. In what kinds of reactions is the chemical similarity between the groups >C=O , >C=S , >C=NR and $\text{—C}\equiv\text{N}$ manifested? What is the cause of this similarity?

3. Why do hydrogen halides, which are easily linked to a double carbon-carbon bond, fail to yield the products of addition to carbonyl compounds?

4. The isotopic exchange between acetone and water containing the isotope O^{18} proceeds very slowly even on heating,

whereas on addition of traces of HCl or of NaOH (10^{-3} to 10^{-5}) the exchange reaction is accelerated even at 25°C . Suggest a mechanism for the exchange in an acidic and an alkaline medium.

5. What factors does the ability of a carbonyl carbon atom to add nucleophilic agents depend on? Arrange the following groups in order of increasing tendency for such addition: $-\text{CHO}$, $-\text{COOH}$, $-\text{COO}^-$, $-\text{CONH}_2$, $-\text{COOCH}_3$, $-\text{COCH}_3$, $-\text{COCl}$.

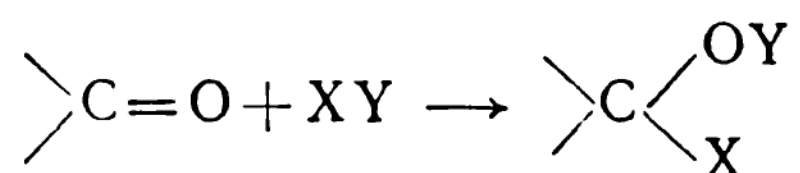
6. What steps are involved in the condensation reaction of carbonyl compounds?

7. What substances can function as the methylene component in condensations of carbonyl compounds?

8. Name methods of activating carbonyl compounds in condensation reactions.

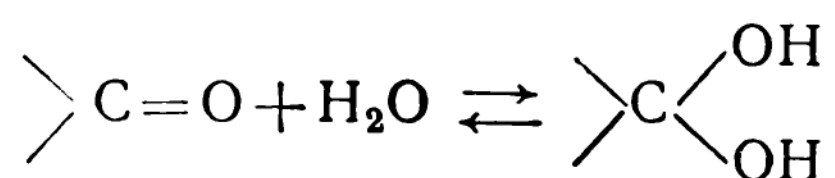
9. Explain how protic acids and Lewis acids contribute to the attack by nucleophilic reagents upon the carbonyl carbon atom.

10. The reactions of addition to the carbonyl group may be represented by the general scheme



Write six reactions with different reagents XY.

11. It is known that carbonyl compounds are capable of forming hydrates with water:



Which compound of each of the following pairs forms a more stable hydrate: (a) propionic aldehyde, $\text{CH}_3\text{CH}_2\text{CHO}$, or methylglyoxal, CH_3COCHO ; (b) acetic or trichloroacetic aldehyde?

12. What compounds are formed by the action of prussic acid, sodium bisulphite and hydroxylamine on methyl ethyl ketone? Explain the mechanism of these reactions.

13. How could you explain the change in the acidity of the medium in the process of cyanohydrin synthesis if a solution of potassium cyanide is used?

14. Why does absolutely pure prussic acid fail to react with aldehydes?

15. Arrange the following compounds in order of increasing rate of cyanohydrin formation: acetone, α -chloropropionic aldehyde, chloral. Write the schemes of these reactions.

16. Arrange the *p*-substituted benzaldehydes of the general formula $X-C_6H_4-CHO$ ($X = H, CH_3, NO_2, Cl, OH$) in order of increasing rate of cyanohydrin formation.

17. Write six reactions of aldehydes that are not characteristic of ketones.

18. Explain why the formation of acetone hydrazone proceeds on mixing the components and the formation of 2,4-dinitrophenylhydrazone requires, in addition, the use of acid.

19. How would you explain the fact that the reaction between semicarbazide and acetone proceeds at a maximum velocity at $pH = 4.5$ and that this velocity decreases with increasing or diminishing pH value?

20. Explain why the formation of semicarbazones does not proceed in hydrochloric acid solution and does so only on addition of sodium acetate, whereas 2,4-dinitrophenylhydrazones are prepared in a strong mineral-acid solution.

21. Explain the following: tautomerism, isomerism, reactions with transfer of reaction centre.

22. Prove the existence of the phenomenon of tautomerism.

23. Explain what happens during the following experiment which is often demonstrated at your lectures: a solution of ferric chloride is added to an aqueous-alcoholic solution of acetoacetic ester and the solution acquires a blue-violet colour. A bromine solution is then carefully added and the initial colour disappears and the brown colour of bromine appears instead. Then this colour also disappears and the solution remains colourless for some time and then regains the blue-violet colour. On addition of bromine the situation repeats itself.

24. In which of the following solvents is acetoacetic ester more enolized: alcohol, hexane, acetic acid, ether?

25. Which of the following compounds is enolized to a greater degree: acetylacetone, acetonylacetone or dibenzoylmethane?

26. To one mole of acetoacetic ester is added a solution of 160 g of bromine in one litre of carbon tetrachloride. What volume of this solution will give a persistent colour due to excess of bromine if it is added under the following conditions: (a) slowly at room temperature; (b) rapidly on cooling to -5°C ?

27. What is the difference in the tendency for enolization between acetylacetone and methyl-*n*-propyl ketone? How would you explain this difference?

28. Will the exchange of hydrogen for deuterium occur readily in diphenylnitromethane on treatment with sodium ethylate in a solution of $\text{C}_2\text{H}_5\text{OD}$?

29. The rate of the bromination of acetone is known to be independent of the concentration of bromine. What assumptions could be made concerning the mechanism of the reaction on this basis?

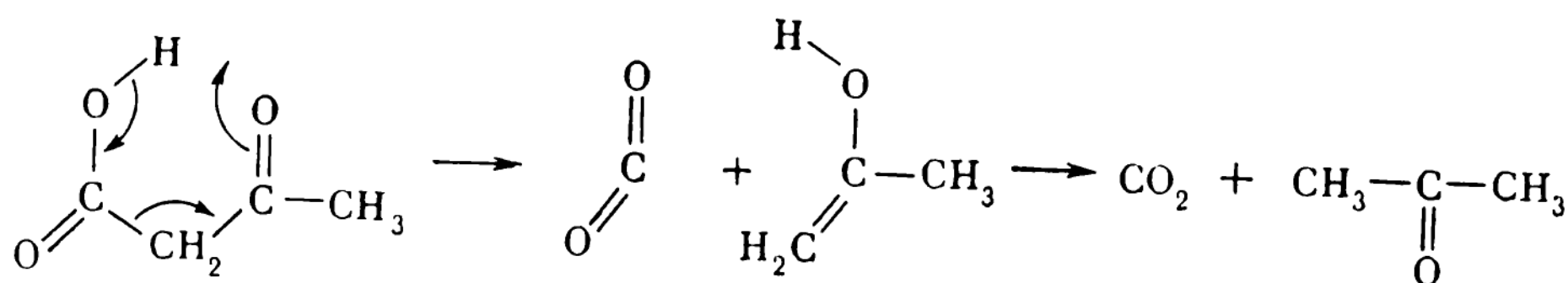
30. Why is optically active phenyl-*sec*-butyl ketone, $\text{C}_6\text{H}_5\text{—CO—CH}(\text{CH}_3)\text{—CH}_2\text{—CH}_3$, racemized on treatment with a base in a hydroxyl-containing solvent?

31. What are the reasons that lead one to choose a base as a condensing agent for the condensations of carbonyl compounds to be carried out?

Under what conditions may one use only catalytic amounts of bases? Under what conditions is it necessary to take them in an equimolecular ratio?

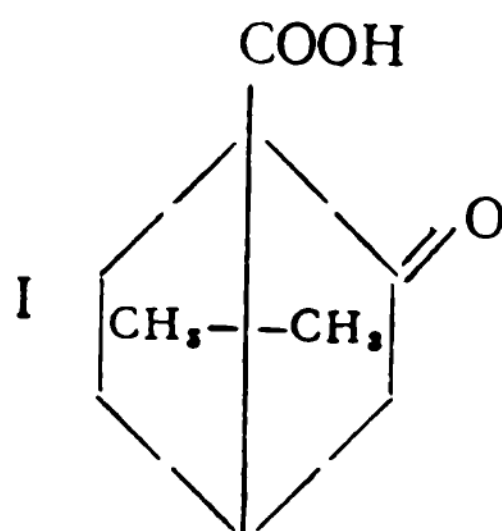
32. Why does acetylacetone form stable complexes with certain metals (for example, bivalent copper) and aceto-nylacetone does not?

33. The following mechanism has been suggested for the decarboxylation of acetoacetic acid proceeding readily at a temperature below 100°C :

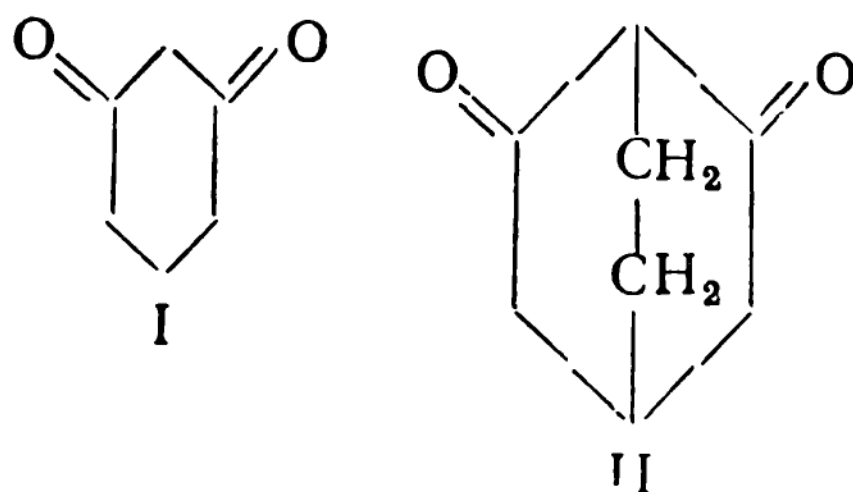


How would you explain, from this point of view, the fact that the decarboxylation of carboxylic acid (I) does

not proceed even at 300° C?



34. A cyclic diketone, cyclohexane-1,3-dione (I), is very readily soluble in aqueous alkali and forms a complex with ferric chloride and with salts of bivalent copper. Bicyclo-[2,2,2]octane-2,6-dione (II) is poorly soluble in aqueous alkali and does not react with iron or copper ions. How would you explain the behaviour of this bicyclic ketone?



2. CONDENSATIONS OF THE ALDOL AND CROTON TYPE

35. Describe the mechanism of aldol-croton condensation under the influence of agents of the acidic and basic nature.

36. Why does the proton in butyraldehyde split off, under the action of sodium ethoxide, more readily from the α -position than from the β - or γ -position?

37. If the aldol condensation of acetone is carried out in the presence of heavy water and stopped before it is complete, the unreacted acetone will contain appreciable amounts of deuterioacetone. Explain why this happens.

38. What steps are involved in the process in which a mixture of formaldehyde and acetaldehyde is converted to pentaerythritol?

39. What substances can be obtained in the aldol condensation of methyl ethyl ketone? Give their names according to IUPAC nomenclature.

40. When a mixture of acetone and ethyl formate is treated with sodium ethoxide in ether, 1,3,5-triacetylbenzene results. What is the scheme of this conversion?

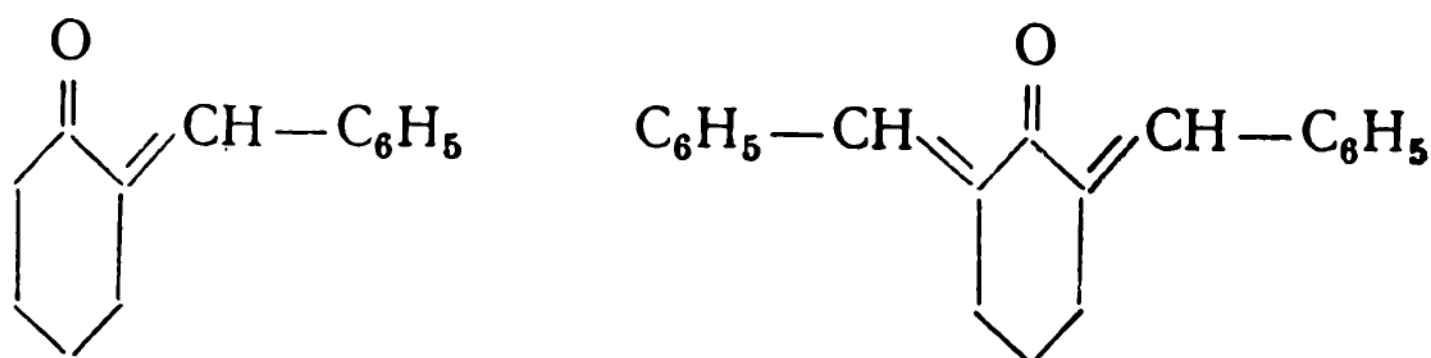
41. What is obtained when furfural is treated with: (a) concentrated solution of sodium hydroxide; (b) an alcoholic solution of potassium cyanide?

42. What is obtained when phenylacetic aldehyde is treated with an alcoholic solution of potassium hydroxide?

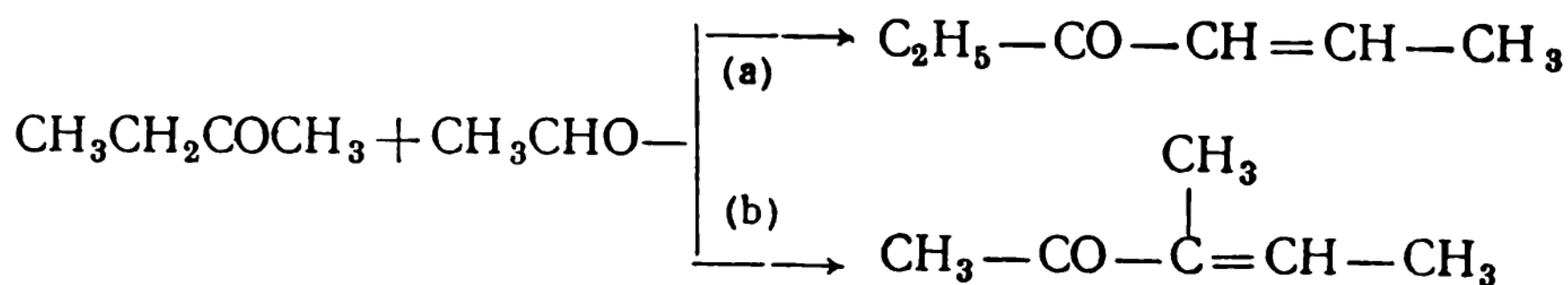
43. What results from the treatment of a mixture of nitroethane and acetaldehyde with a concentrated solution of sodium hydroxide?

44. How can the following compounds be prepared from acetaldehyde: (a) 1,1-dichloro-2,3-dibromobutane; (b) 3-chlorobutyraldehyde?

45. Why does the reaction of cyclohexanone with benzaldehyde result largely in the formation of the compounds (I) and (II) and not of the product of self-condensation of cyclohexanone?



46. The condensation of aldehydes with methyl alkyl ketones leads to the formation of two products, for example,



How can the reaction be directed predominantly: by the route (a) or (b)?

47. How can 1,3,5-trimethylbenzene (mesitylene) and 1,3,5-triphenylbenzene be obtained by means of a croton condensation?

48. What compound must be taken for condensation with benzaldehyde in order to obtain, as a result of subsequent conversions, 1-phenyl-2-aminopropane-1,3-diol, an intermediate product in the synthesis of the antibiotic Chloromycetin?

49. Why is the condensation of desoxybenzoin with benzaldehyde effected by the action of gaseous hydrogen chloride rather than of alkaline reagents? What is the course of this reaction?

50. On heating isobutyraldehyde with barium hydroxide the product of aldol condensation is not formed. Instead, the barium salt of isobutyric acid and isobutyl alcohol are formed. Explain this phenomenon.

51. The condensation of acetone to diacetone alcohol is carried out by the action of barium hydroxide placed in the case of Soxhlet apparatus. Explain why this experimental procedure has to be used.

3. ESTER CONDENSATION AND RELATED REACTIONS

52. What condensing agents of the basic nature are used to effect an ester condensation? Name six such reagents at least and arrange them in order of increasing condensing action.

53. Explain why the ester condensation of ethyl acetate may be accomplished with the aid of sodium ethoxide or sodium amide, whereas the condensation of ethyl isobutyrate has to be carried out with triphenylmethyl sodium.

54. What will be the result of the action of a solution of sodium ethoxide on ethyl isovalerate, isopropyl propionate, ethyl isobutyrate, isobutyraldehyde, and benzaldehyde?

55. How can an ester condensation be brought about to prepare 1-methyl-3-carbethoxy-4-piperidone?

56. How can the diethyl α,α' -dicarbethoxysuccinate be produced? What properties does it possess?

57. How can benzoylacetone be obtained? What are its properties?

58. Which of the following methods will be more conveniently used for synthesis of benzoylacetic ester: (a) the action of sodium ethoxide on a mixture of ethyl acetate and ethyl benzoate; (b) the treatment of a sodium derivative of acetoacetic ester with benzoyl chloride?

59. How can formylacetic ester be prepared? What properties does it possess?

60. How can acetoneoxalic ester be obtained? What properties does it possess?

61. What compound will be produced by the action of sodium ethoxide on ethyl phenylacetate?

62. Synthesize 2,3,4,5-tetraphenylcyclopentadienone from phenylacetic acid and benzaldehyde.

63. How can diethyl phenylmalonate be prepared?

64. What substance will be obtained by the action of sodium alkoxide on diethyl adipate? How does the resulting product respond to the action of acids and bases?

65. Diethyl adipate was successively subjected to the action of sodium ethoxide metallic sodium, and methyl iodide. Part of the resulting product was subjected to acid splitting, and part to ketonic splitting. Write the schemes of these reactions.

66. How can the following compounds be prepared: (a) dibenzoyl methane; and (b) acetylacetone?

67. What substances result from the condensation of ketones with the esters of α -halogeno-substituted acids or with α -haloketones?

68. What substance is formed by the action of sodium ethoxide on a mixture of benzaldehyde and α -chloroacetone?

69. Write the scheme of condensation of a mixture of cyclopentanone and ethyl formate under the action of sodium ethoxide.

70. What is the course of the reaction between ethyl butyrate and ethyl benzoate in the presence of sodium amide?

71. How can the following compounds be prepared: (a) cinnamic acid; (b) pent-3-en-2-one; (c) benzylacetone; (d) 5-phenylpenta-2,4-dienic acid; (e) 1,4-diphenylbuta-1,3-diene; (f) 1-aminomethyl-2-ethylcyclohexanol; (g) 5-phenylpenta-2,4-dienol; (h) 1,2-diphenylethylene?

4. SYNTHESSES WITH ACETOACETIC AND MALONIC ESTERS

72. Explain why on alkylation of 1 mole of sodiomalonic ester with 1 mole of methyl iodide, in addition to methylmalonic ester, there is formed dimethylmalonic ester, an equivalent amount of unalkylated malonic ester being left.

73. Prepare isovaleric acid and methyl isopropyl ketone from acetoacetic ester.

74. Prepare 1-methylcyclohex-1-en-3-one from acetoacetic ester and formaldehyde.

75. Ketones obtained by acetoacetic ester syntheses always give a haloform reaction. How would you explain this?

76. Why is it more convenient to use malonic and not acetoacetic ester for the synthesis of acids?

77. How can α,α' -dimethylsuccinic acid be prepared from malonic ester?

78. How can α -methylglutaric acid be obtained from malonic ester?

79. How can the following compounds be produced from acetoacetic ester: (a) benzylacetone; (b) γ -acetylpropionic acid; (c) acetonylacetone?

80. The successive action of sodium ethoxide *n*-propyl bromide, sodium amide, isopropyl bromide, and barium hydroxide on acetoacetic ester led to the formation of a compound of the composition $C_9H_{18}O$. This compound forms crystalline precipitates with semicarbazide, aniline, and does not react with silver oxide. What is its structure?

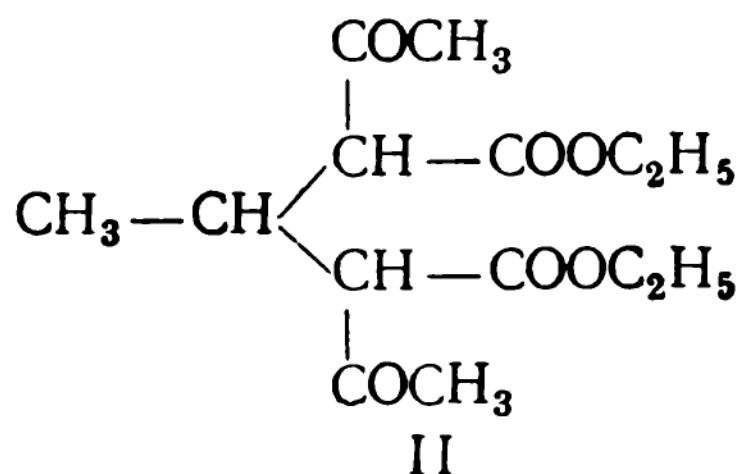
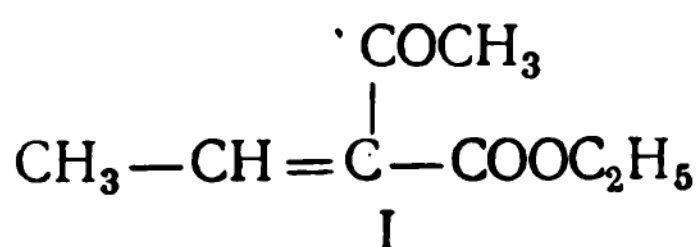
81. Synthesize the following compounds from acetoacetic or malonic ester: (a) methylpropylacetic acid; (b) dimethylacetic acid; (c) succinic acid; (d) methyl isoamyl ketone; (e) acetylacetone; (f) acetonylacetone; (g) 3,4-dimethylhexane-2,5-dione; (h) 3,4-isopropylhexane-2,5-dione; (i) ethylsuccinic acid; (j) ethylene ketal of methyl ethyl ketone; (k) α -methyllevulinic acid.

5. REACTIONS OF CARBONYL COMPOUNDS

82. Suggest methods of preparing esters of the enol forms of acetaldehyde and acetone.

83. *p*-Tolualdehyde was treated with a solution of potassium cyanide. What compound was formed?

84. How would you explain the fact that the reaction between acetaldehyde and acetoacetic ester in the presence of weak bases results in the formation of the compounds I and II?



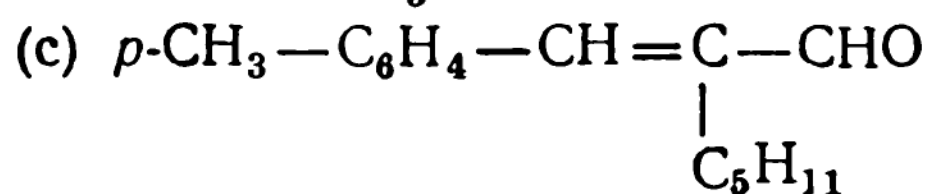
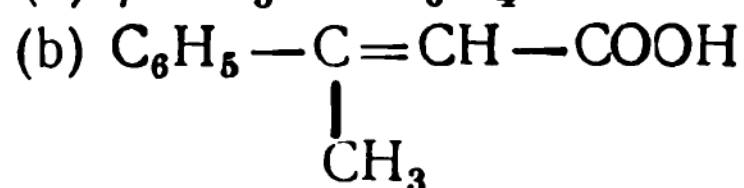
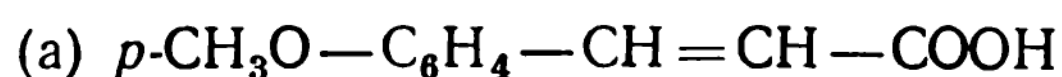
85. In what order does the rate of acid splitting of the following compounds change: diethyl ether, acetaldehyde diethylacetal, and *ortho*-ethyl acetate?

86. Three test tubes contain 1,1-, 2,2- and 1,3-dimethoxypropanes, respectively. How could you identify each of these compounds?

87. It is known that the action of iodine and alkali on ethyl alcohol (ethanol) gives iodoform. The same substance can be derived from other compounds too. What structural features must a compound possess in order to form iodoform?

88. Suggest two methods for preparation of sorbic acid, $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{COOH}$, in which the condensation reactions of acetaldehyde could be used.

89. Using the condensation reactions of carbonyl compounds, prepare the following:



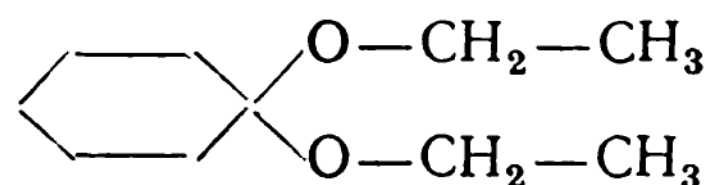
90. How could the following conversion be accomplished¹: $\text{C}_6\text{H}_5-\text{CHO} \rightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CHO}$?

91. How can α -methylphenylacetaldehyde be derived from acetophenone¹?

92. Prepare the following substances by using available carbonyl compounds: (a) 3-phenylpent-1-yn-3-ol; (b) 1-ethylcyclohexanol; (c) hex-3-yne-2,5-diol.

¹ Make use of the Darzens reaction.

93. How will the following compound respond to the action of acids and bases?

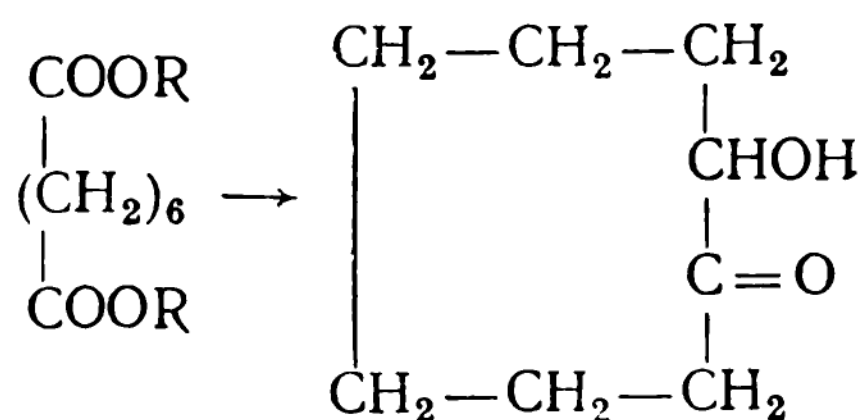


94. How can α -methylalanine (α -aminoisobutyric acid) be synthesized from acetone?

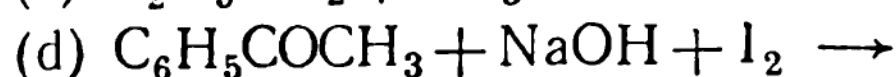
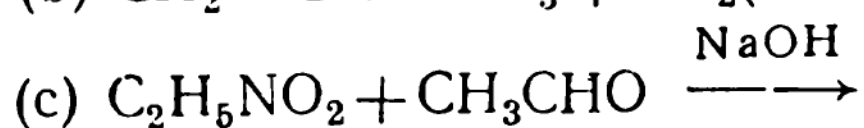
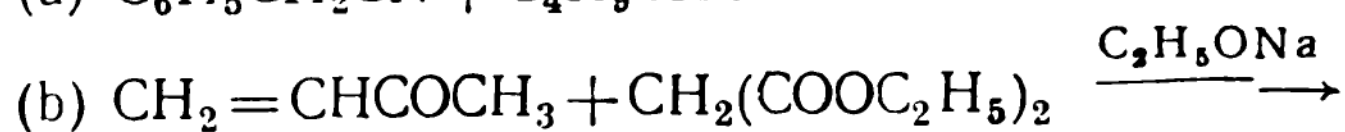
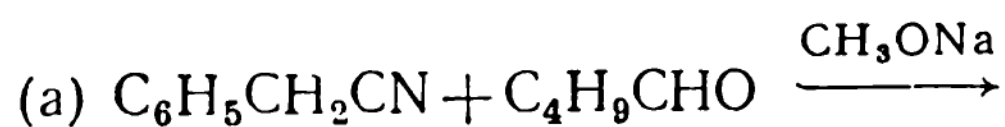
95. How can benzaldehyde be converted to mandelic acid, $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{COOH}$?

96. What substance is formed by the reaction between malonic acid and benzaldehyde in the presence of a weak base?

97. By means of what reagents and under what conditions can the following conversion be accomplished?



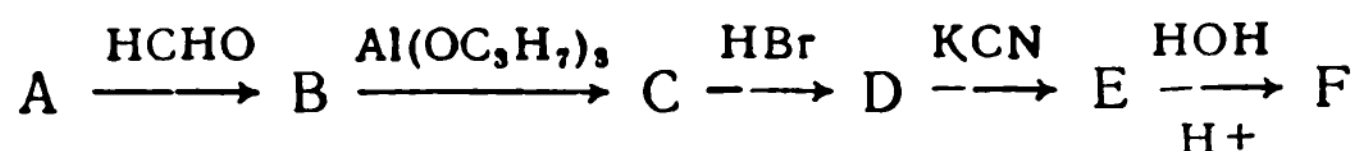
98. What is the principal route of the following reactions?



99. How can the following compounds be derived from *p*-methoxybenzaldehyde: (a) *p*- $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CHOH}-\text{COOH}$; (b) *p*- $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CHOH}-\text{C}_2\text{H}_5$; (c) *p*- $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CHNH}_2-\text{COOH}$; (d) *p*- $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{COOC}_2\text{H}_5$; (e) *p*- $\text{CH}_3\text{OC}_6\text{H}_4-\text{CH}=\text{N}-\text{N}=\text{CH}-\text{C}_6\text{H}_4\text{OCH}_3$ -*p*?

100. By using the Perkin reaction one can derive cinnamic acid from benzaldehyde, acetic anhydride and sodium acetate. What considerations can be advanced in favour of the anhydride being condensed with the aldehyde and not with sodium acetate?

101. Identify the following scheme of conversions:



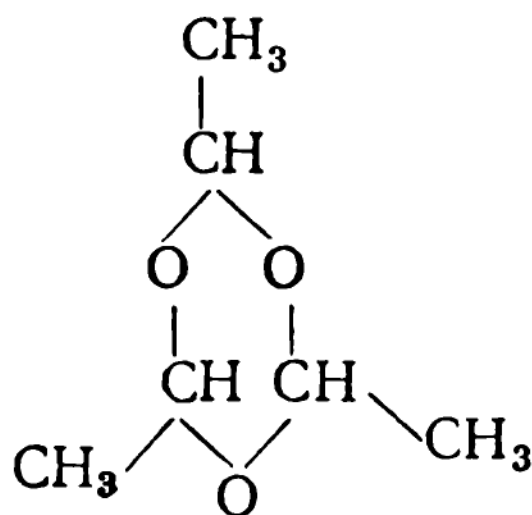
The letter F stands for α -methylglutaric acid.

102. How can a compound having the structure $\text{CH}_3\text{COCH}_2\text{-CH}_2\text{N(C}_2\text{H}_5)_2\cdot\text{HCl}$ be derived from acetone?

103. What substance is formed by heating a mixture of acetophenone, paraform, and piperidine?

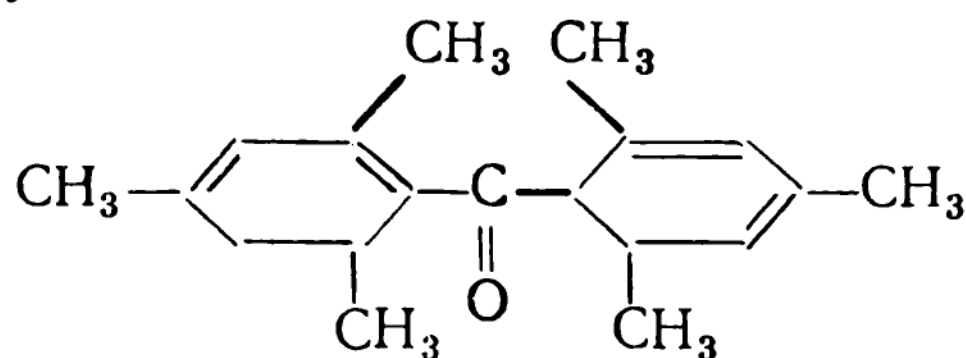
104. What compound results on heating a mixture of diethyl ketone, paraform, and dimethylamine?

105. What is the attitude of a compound having the following structure to the action of acids and bases?



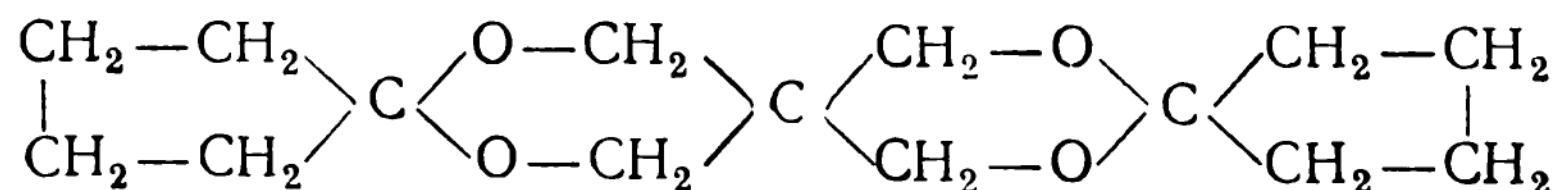
What is the name of this compound and how can it be prepared?

106. Dimesityl ketone



is practically incapable of entering into reactions that are usually characteristic of carbonyl compounds. What is the cause of the inertness of the carbonyl group in this ketone?

107. Suggest a single-stage synthesis whereby a compound having the structure indicated below could be obtained from simple starting substances.



How does this compound respond to the action of acids and bases?

108. How does acetone react with acrylonitrile in the presence of alkaline catalysts?

109. How does mesityl oxide react with methylamine?

110. How could you account for the fact that hexamethylacetone is incapable of forming an oxime?

111. How does the compound called "Girard's reagent T" react with carbonyl compounds? This reagent has the following structure:



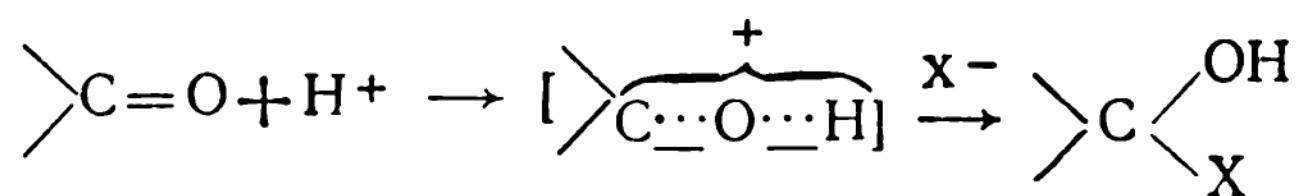
112. How would you explain the fact that the hydrogen of the CH_2 group of the ester of glutaconic acid, $\text{H}_5\text{C}_2\text{OOC}-\text{CH}=\text{CH}-\text{CH}_2-\text{COOC}_2\text{H}_5$, is capable of being displaced by alkyl on successive treatment with sodium methoxide and an alkyl halide, i.e., being alkylated like acetoacetic and malonic esters?

Answers

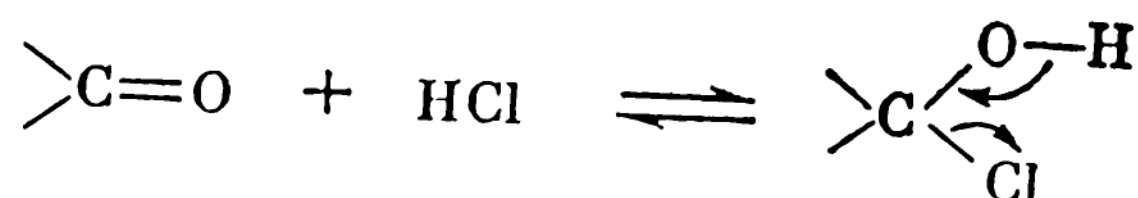
1. See introduction to the present chapter.

2. A common feature of the groups $>\text{C}=\text{O}$, $>\text{C}=\text{S}$, $>\text{C}=\text{NR}$, and $-\text{C}\equiv\text{N}$ is the polarization of the carbon-element bond. As a result of this polarization, a partial positive charge appears on the carbon atom, this charge being responsible for reactions with nucleophilic reagents and capable, by its action on hydrogen atoms, of increasing their ability to split off in the form of protons.

3. Being strongly polar reagents, hydrohalic acids add on readily to the polarized $\text{C}=\text{O}$ bond according to the scheme



The addition products, being analogues of *gem*-dihydroxyl compounds (1,1-diols), are however rather unstable and decompose into the original substances:



This equilibrium is strongly shifted to the left.

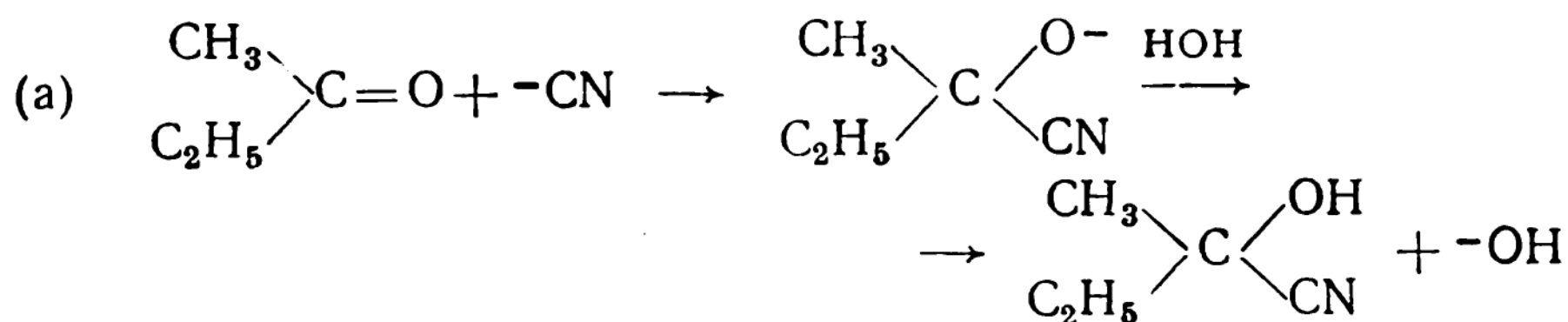
can the charge in the anion formed be delocalized due to the neighbouring carbonyl oxygen (see the equation given above).

The bases used are alkali metals, alkalis, alkoxides, sodium amide, sodium hydride, triphenylmethylsodium, and mesitylmagnesium bromide (see Chapter 6).

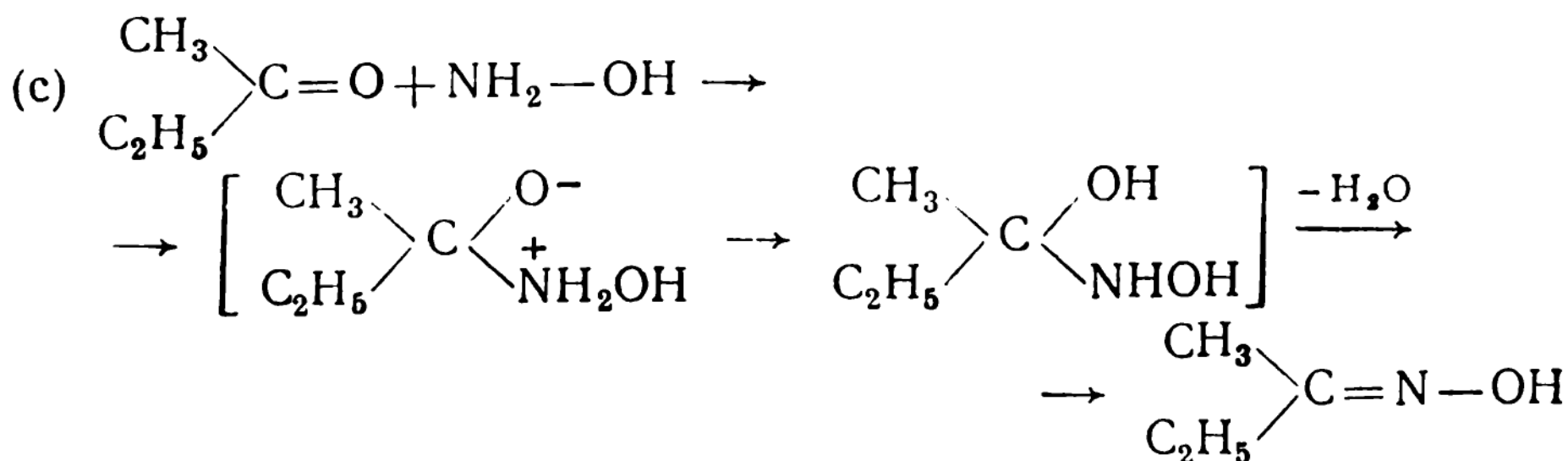
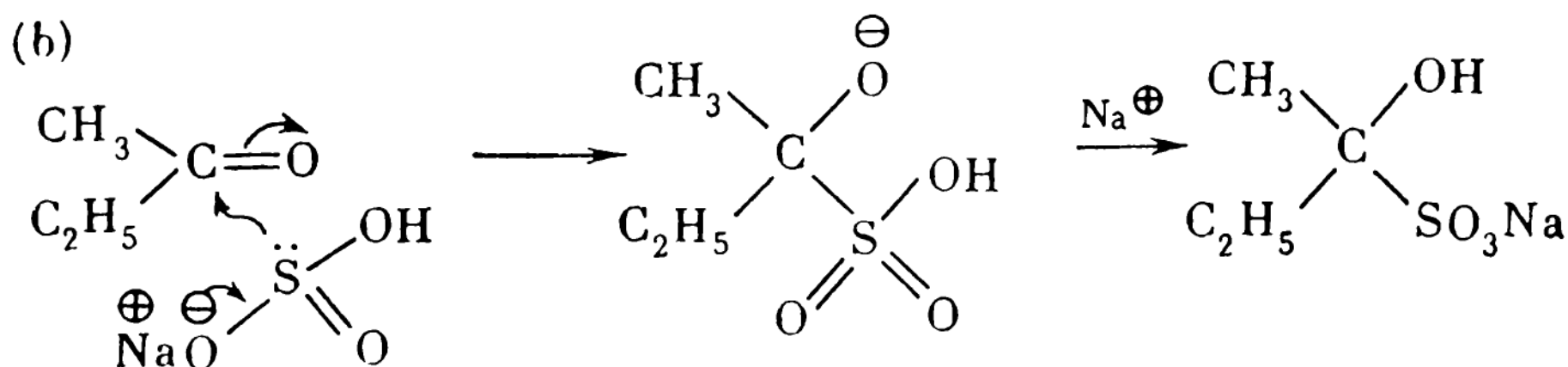
10. The addition of hydrogen, water, alcohols, mercaptans, prussic acid, and sodium bisulphite.

11. The stability of hydrates increases with increasing magnitude of the positive charge on the carbonyl carbon atom. That is why the stability of methylglyoxal and trichloroacetaldehyde is higher.

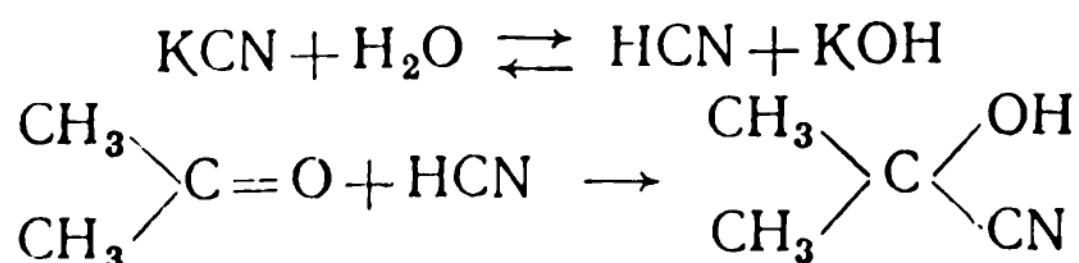
12.



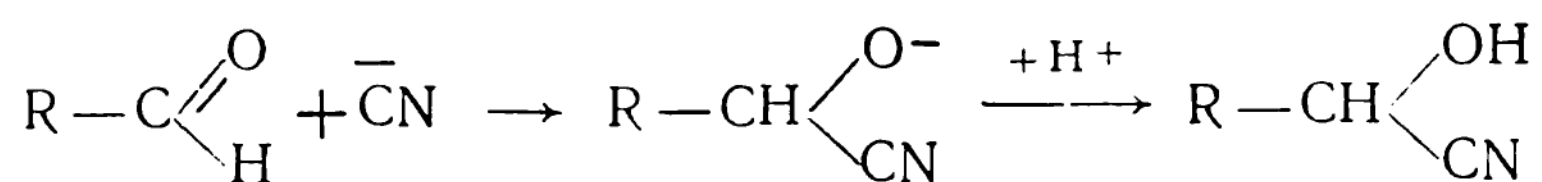
(see also the explanation to Problem 14)



13. The pH value of the medium during the cyanohydrin synthesis under the conditions indicated increases owing to the following reactions:



14. The addition of prussic acid at the carbonyl group is an example of a reaction proceeding under the influence of a strong nucleophile (the cyanide ion, in this case). Hydrogen cyanide itself is an undissociated compound, which forms no cyanide ions and does not add on to the CO group. In the presence of bases, however, it does dissociate and the reaction proceeds by the usual scheme (see also answer to the previous problem):



15. Acetone < α -chloropropionaldehyde < chloral.

16. $\text{OH} < \text{CH}_3 < \text{H} < \text{Cl} < \text{NO}_2$.

17. Reaction with fuchsinsulphuric acid; oxidation reaction (including the silver mirror reaction); Tishchenko reaction; Cannizzaro reaction; benzoin condensation; the formation of primary alcohols on reduction.

18-20. The added acid activates the carbonyl compound

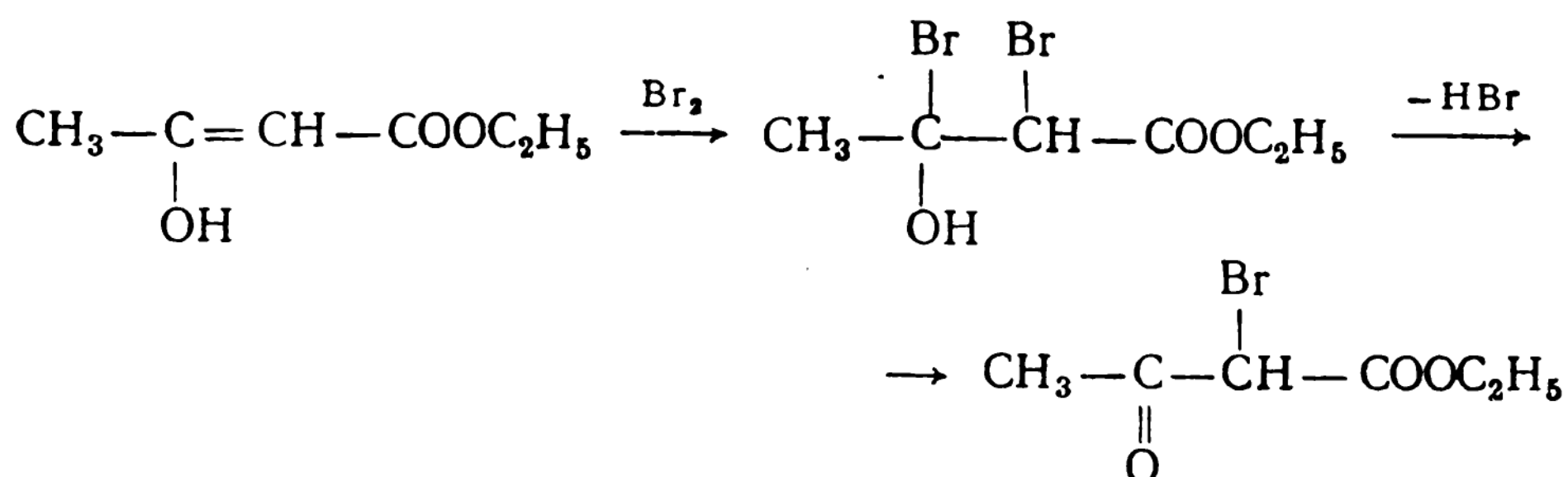
(proton addition: $\text{>C=O} + \text{H}^+ \rightleftharpoons \text{>}\overbrace{\text{C}^+\cdots\text{O}\cdots\text{H}}^+$), but at the same time it binds the base-reagent in the form of a salt and reduces its activity; therefore there always exists a region of the optimal pH value. The weaker is the reagent as a base, the more acidic can the medium be made without the risk of converting it into a salt.

21. See A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 1, pages 185-189, 251-259, 413-431; and O. Reutov, *Theoretical Principles of Organic Chemistry*, Chapter X.

22. A confirmation is provided by experiments carried out with acetoacetic ester: substances having the keto and enol structures can be isolated in pure form (there are several methods for this); one can then make sure that each of the isomers enters into reactions characteristic only of a given form and is gradually converted, when allowed to stand, into "ordinary" equilibrium acetoacetic ester which gives reactions of both forms.

23. A blue-violet colour with ferric chloride is imparted by the enol form of acetoacetic ester. The added bromine

immediately reacts with the enol form:



As soon as the enol form is used up its colouration with ferric chloride disappears, excess bromine is formed, which is detected by the brown colour. Since there exists an equilibrium between the keto and enol forms, part of the keto form is converted into the enol form, and the latter decolorizes the excess bromine and then gives the blue-violet colour with the ferric chloride present.

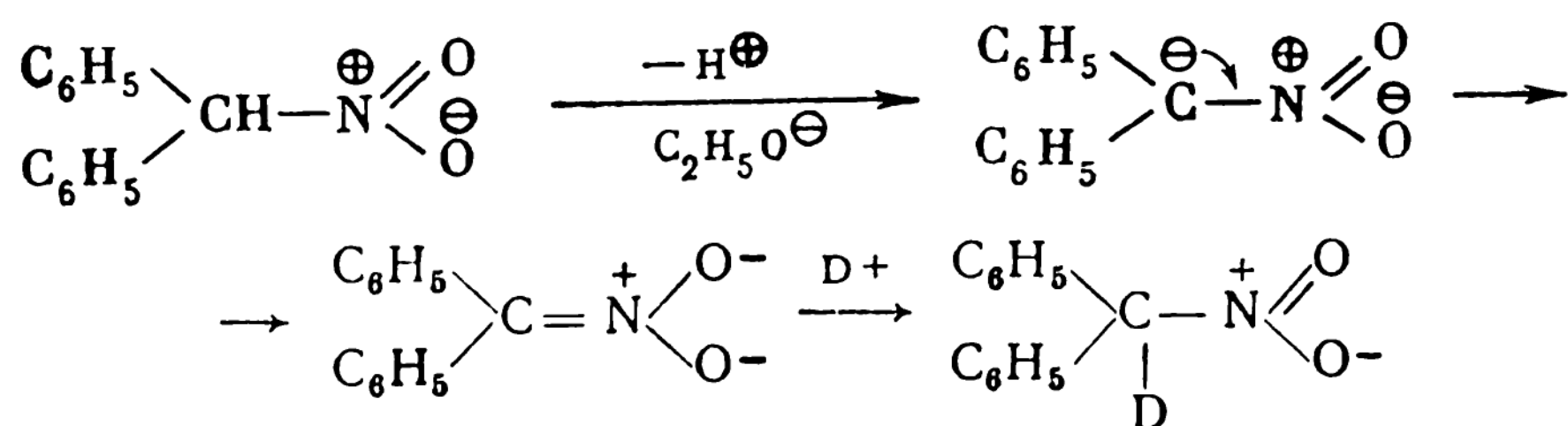
24. Hexane > ether > alcohol > acetic acid (see A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 1, page 419 and J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965).

25. Dibenzoylmethane > acetylacetone >> acetonylacetone.

26. On gradual addition at room temperature 1 litre of the bromine solution will be used up (the entire amount of acetoacetic ester is gradually enolized and reacts with the bromine), and on rapid addition at -5°C about 70 ml will be consumed, which corresponds to 7% of the enol content.

27. See the literature in answer to Problem 21.

28. As a result of the tautomeric conversion of the nitro compound to the aci-form, the exchange of hydrogen of the methine for deuterium is easily accomplished:



At a small concentration of the nitro compound in the solution of $\text{C}_2\text{H}_5\text{OD}$ the exchange occurs practically completely.

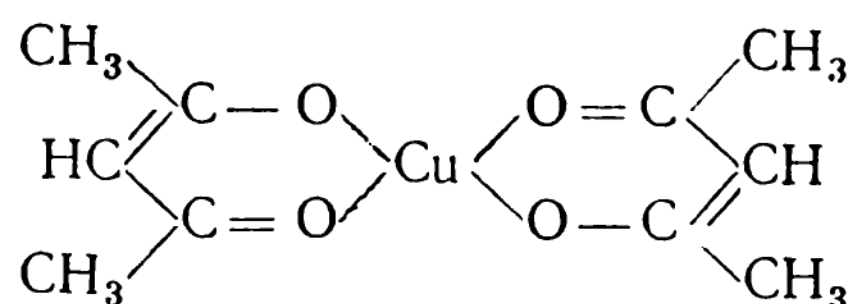
29. That the rate of bromination of acetone is independent of the bromine concentration indicates that bromine does not take part in the slowest, rate-determining, step of the reaction. This step is supposed to be the enolization of acetone.

30. When phenyl-*sec*-butyl ketone is treated with a base, an equilibrium is set up between the keto and enol forms in the hydroxyl-containing solvent.

This process involves the asymmetric carbon atom (there is no asymmetric carbon atom in the enol form) and there occurs racemization.

31. The base used must be somewhat stronger than (or at least as strong as) the anion formed from the methylene component. If the anion of the condensation product is a stronger base than the condensing agent used, then catalytic amounts of the latter are sufficient for the reaction to proceed to completion (since the condensing substance is regenerated in the course of the process).

32. The copper complex of acetylacetone has a chelate structure:

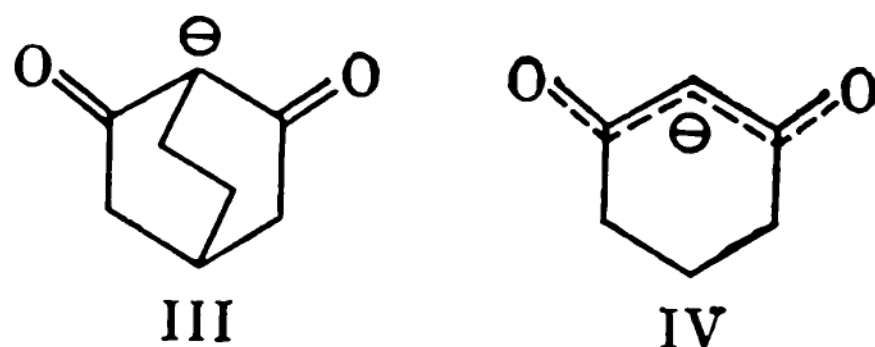


Acetonylacetone is incapable of forming such a chelate compound (because of the negligibly low enolization and the difficulties involved in the formation of a seven-membered ring).

33. The decarboxylation of acetoacetic acid involves the stage of formation of its enol form. Camphorcarboxylic acid (I) cannot be enolized on the grounds of Bredt's rule (which states that a double bond cannot be formed by a carbon atom occupying the bridge-head).

34. If the carbanion (III) were formed from the bicyclic diketone (II), the charge could not have been delocalized in the former because a rigid bicyclic structure cannot become planar. That is why the compound (II) shows no tendency to be converted into the carbanion (III). As to the ability to dissolve in alkali and to react with ions of heavy metals, it is determined by the ease with which the carbanion is formed. The planar anion (IV) with a delocalized charge is formed without difficulty from cyclohexane-1,3-dione (I)

and this diketone dissolves readily in alkali and reacts with ions of heavy metals:



The formation of a coloured complex with ferric chloride is characteristic of enols. Cyclohexane-1,3-dione (I) yields rather readily the corresponding enol, whereas bicyclo[2,2,2]-octane-2,6-dione (II) gives no enol at all because it must have contained a double bond at the bridge-head (according to Bredt's rule).

35. See A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 1, page 148 and J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

36. See answers 9 and 34.

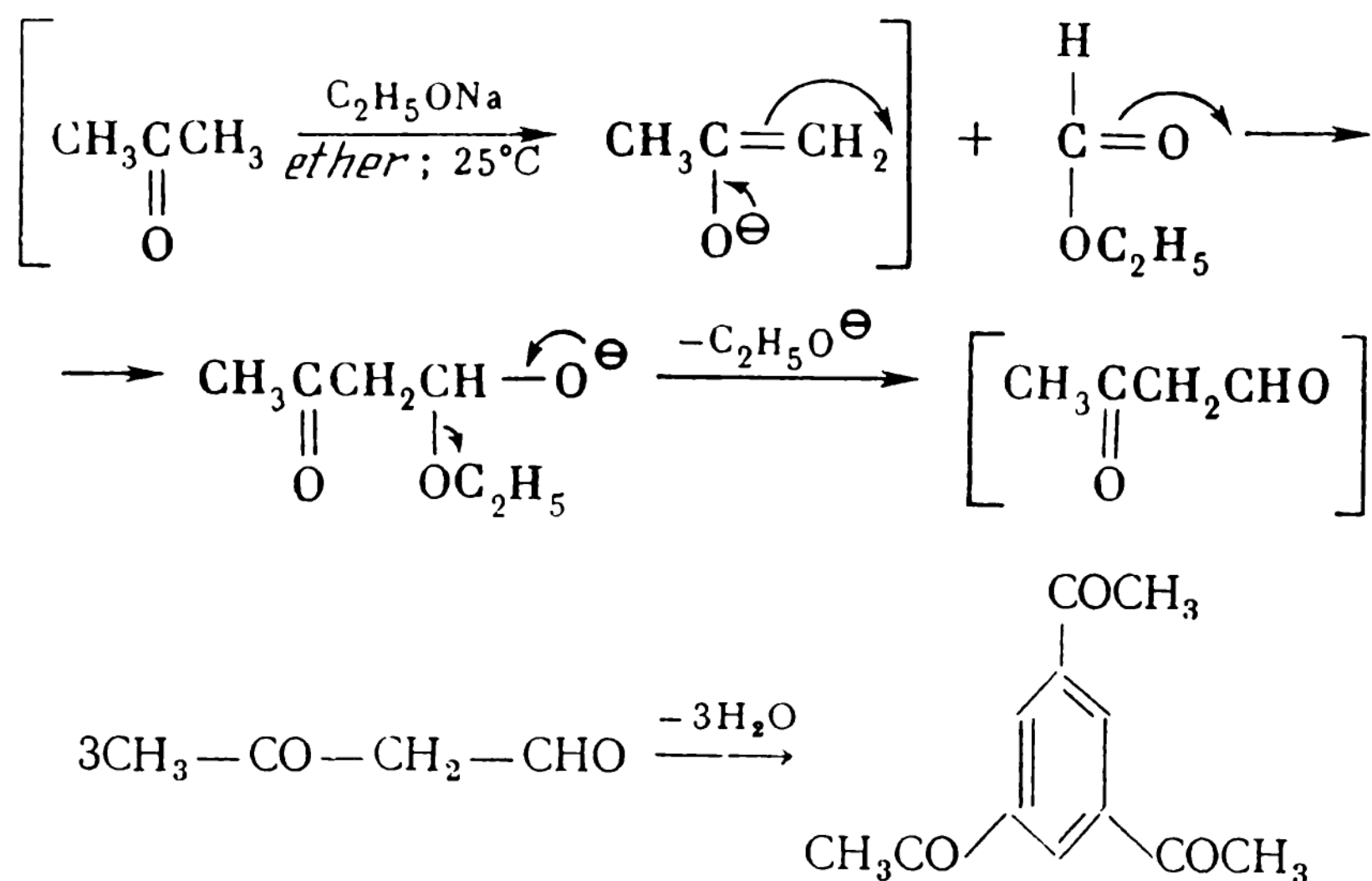
37. The aldol condensation is carried out in the presence of bases. In this process, acetone (like other aldehydes and ketones) is converted to the enolate ion. The latter may either react with the unenolized molecule of acetone (aldol condensation) or, as a result of the interaction with the heavy water present in the reaction mixture, be converted to deuterioacetone. Since both reaction routes are accomplished simultaneously, the reaction mixture always contains, in addition to diacetone alcohol, deuterioacetone.

38. The formation of pentaerythritol involves two steps: (a) the aldol condensation of three molecules of formaldehyde (the carbonyl component) with one molecule of acetaldehyde (the methylene component); (b) the "crossed" Cannizzaro reaction, as a result of which the trihydroxyaldehyde formed is reduced by the formaldehyde molecule, which is converted to a formate ion.

39. The aldol condensation of methyl ethyl ketone is effected by the action of reagents of a basic character (when acidic reagents are used, the products of croton condensation are usually formed). In this process the initial splitting off of a proton occurs predominantly from the methyl group of methyl ethyl ketone rather than from the methylene group,

in which the electron density on the carbon atom is higher due to the electron-donating effect of the methyl group attached to it. The principal direction of the reaction is therefore the formation of 3-hydroxy-3-methylheptan-5-one, though there may also be formed a second possible product of aldol condensation, 4-hydroxy-3,4-dimethylhexan-2-one.

40. First, a rather reactive dicarbonyl compound, formylacetone, is formed, which then undergoes self-condensation:



41. (a) Under the action of a concentrated solution of sodium hydroxide, furfural, being an aromatic aldehyde, enters into the Cannizzaro reaction, yielding furyl alcohol and pyromucic acid (furan-2-carboxylic acid).

(b) Under the action of an alcoholic solution of potassium cyanide there is formed furoin (benzoin-type condensation).

42. Three molecules of phenylacetic aldehyde react with one another by way of a croton-type condensation with ring closure and formation of 1,3,5-triphenylbenzene.

43. There takes place an aldol-type condensation with nitroethane, which functions as the methylene component. The reaction product is 3-nitrobutan-2-ol.

The concomitant reaction is the self-condensation of acetaldehyde with the formation of crotonaldehyde, higher condensation products, and resins. For a nitro alcohol to be obtained in good yield it is necessary that the optimal conditions be strictly maintained.

44. (a) Acetaldehyde is converted to crotonaldehyde, which is subjected first to the action of bromine and then to that of phosphorus pentachloride.

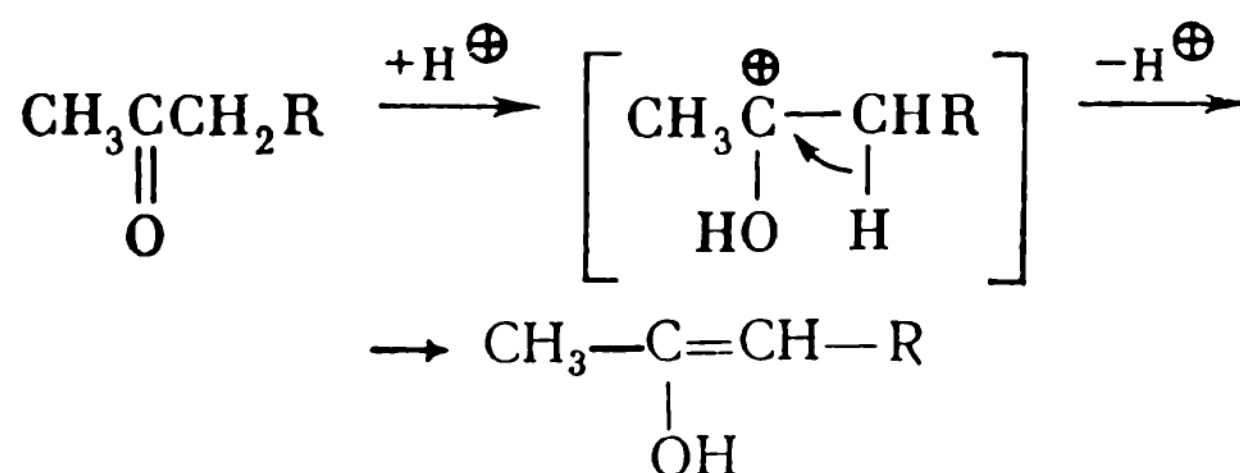
(b) To crotonaldehyde is added hydrogen chloride.

45. Aldehydes, and particularly benzaldehyde, are more active carbonyl components (they bear a higher positive charge on the carbonyl carbon) than ketones.

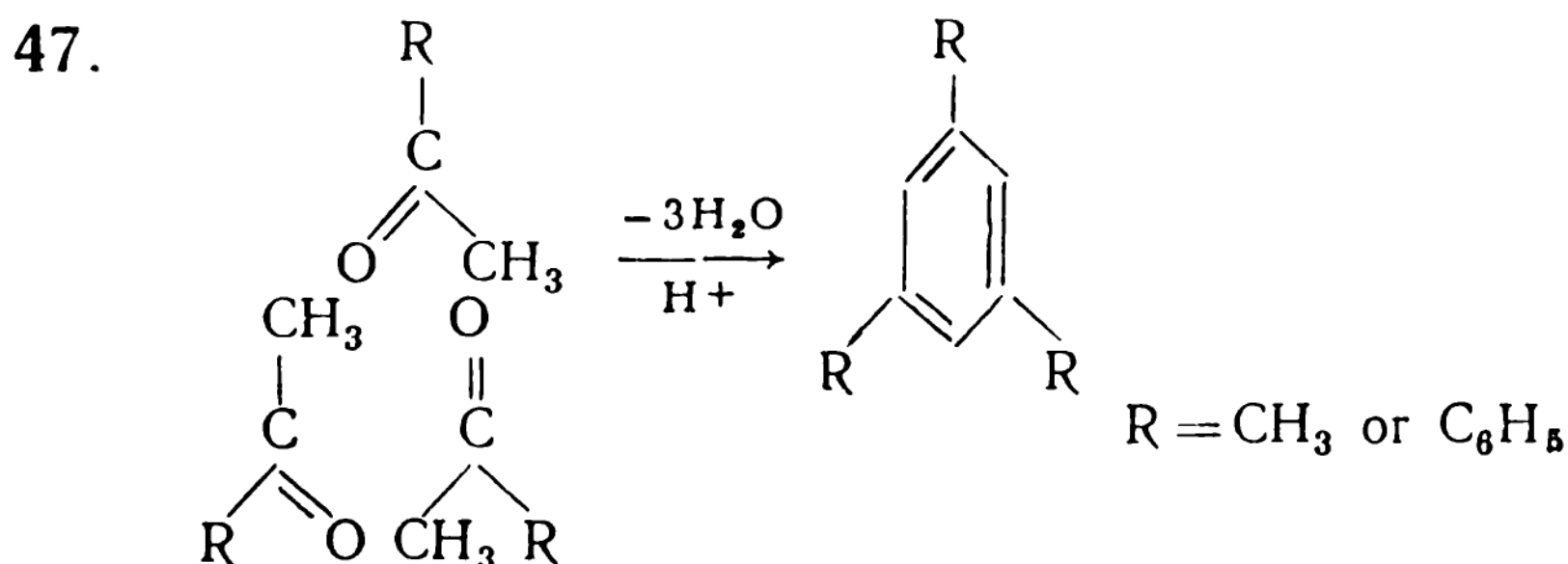
46. Acetaldehyde (and aldehydes in general) serves as the carbonyl component in the reaction (answer 45).

The route of the reaction is determined by the direction of the enolization of methyl alkyl ketone. In the presence of bases the enolization is effected predominantly through the expulsion of a proton from the methyl group (see answer 39) and, depending on the conditions, may end with the formation of the products of aldol- and croton-type condensations (path *a*).

In the presence of acidic catalysts (for example, protic acids) the enolization leads to the formation of the most substituted enol.



and, consequently, the condensation takes the route *b*. As is always the case with acidic reagents, this condensation is of the croton type.

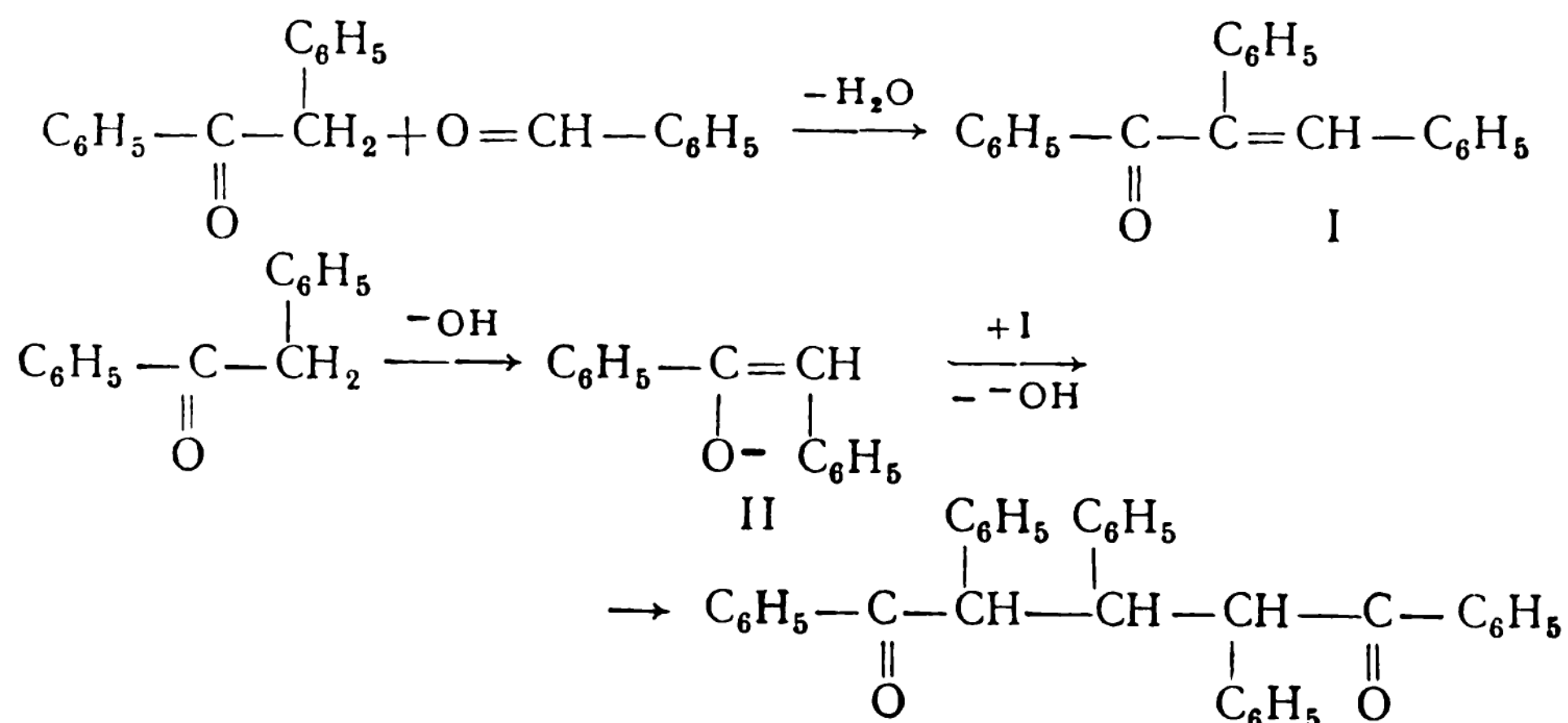


In the preparation of mesitylene ($\text{R} = \text{CH}_3$), the source of protons is concentrated sulphuric acid. When 1,3,5-triphenylbenzene ($\text{R} = \text{C}_6\text{H}_5$) is to be produced, acetophenone is

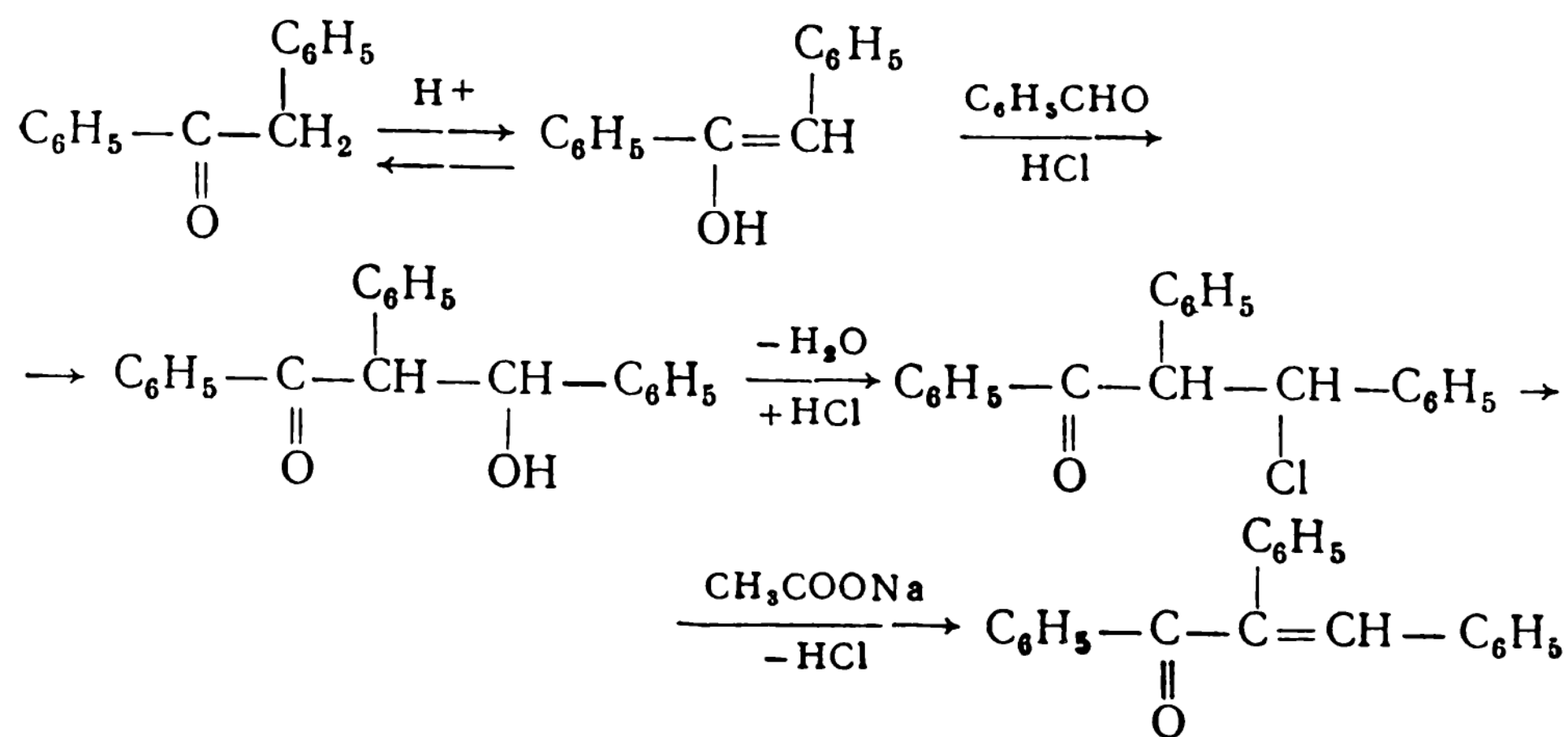
heated with aniline chloride (when heated it dissociates to form hydrogen chloride).

48. Benzaldehyde is condensed with 2-nitroethyl alcohol by the aldol mechanism and the nitro group in the product obtained is reduced to the amino group.

49. In a strongly alkaline medium, benzaldehyde undergoes a Cannizzaro reaction. In a weakly alkaline medium, the α -, β -unsaturated ketone (I) formed at the first stage adds to desoxybenzoin (II), which is the methylene component:



For this reason the benzylidene derivative of desoxybenzoin is prepared by the passage of dry hydrogen chloride through a mixture of both reagents, whereby the following reaction is effected:



50. The anion formed on removal of the proton from the α -position in isobutyraldehyde is a stronger base than ba-

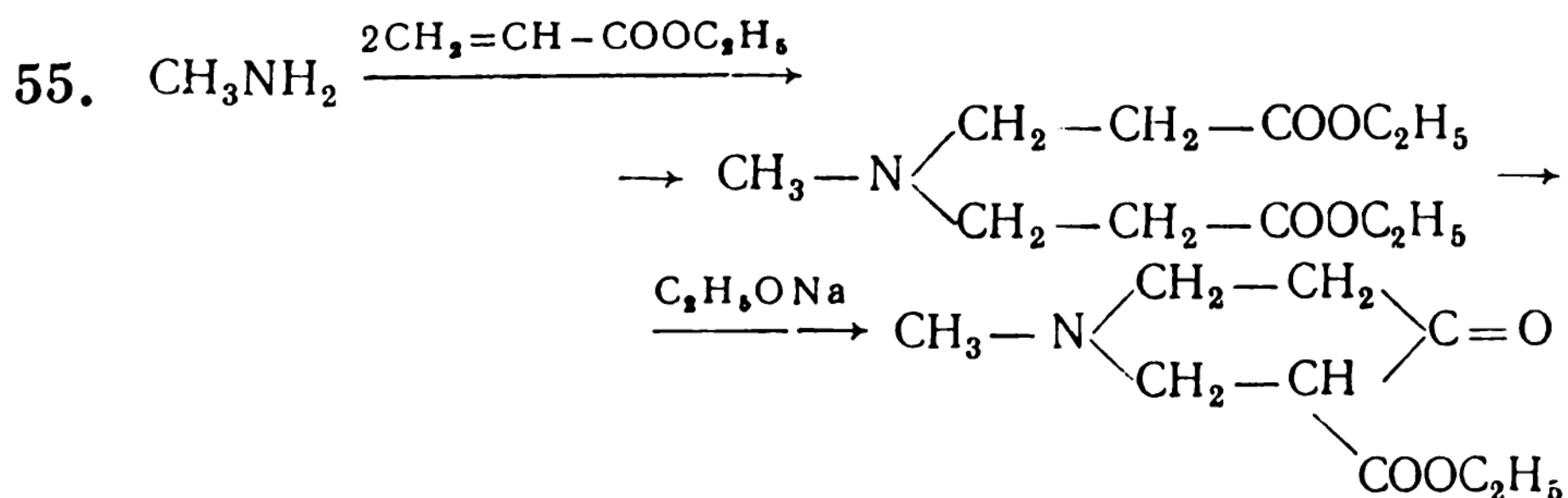
rium hydroxide (see answers 31 and 53). Thus, in this case the proton cannot be removed by the action of $\text{Ba}(\text{OH})_2$. Instead of the aldol condensation the Cannizzaro reaction is effected.

51. In the case of the Soxhlet apparatus, under the action of an alkaline condensing agent, barium hydroxide, there is set up an equilibrium between acetone and the product of its aldol condensation—diacetone alcohol (the content of the latter in the equilibrium mixture is about 5 per cent). Then this liquid is siphoned into the flask, wherefrom acetone is gradually distilled out into the beaker containing the case, and the difficultly volatile diacetone alcohol remains in the flask and is no longer in contact with the alkaline catalyst, which could have caused further condensation or decomposition.

52. $\text{NaOH} < \text{CH}_3\text{ONa} < (\text{CH}_3)_3\text{CONa} < (\text{C}_6\text{H}_5)_3\text{CNa} < \text{NaNH}_2 < \text{NaH}$.

53. The expulsion of a proton from the α -carbon atom of ethylisobutyrate is hindered because of the effect of two neighbouring methyl groups (steric factors may possibly also play a part here: the reaction centre in this case is a tertiary carbon atom). The anion formed as a result of this proton expulsion is a stronger base than the ethoxide anion, the latter being therefore incapable of generating it. Use has to be made of one of the strongest bases—triphenylmethylsodium. This base is used up irreversibly (it is converted to triphenylmethane) and it must therefore be taken in equimolecular quantities.

54. Ethyl isovalerate and isopropylpropionate will undergo an ester condensation, and ethylisobutyrate will remain unchanged (see answer 53); isobutyraldehyde (see answer 50) and benzaldehyde will engage in the Cannizzaro reaction.



56. From diethyl malonate there is obtained a sodium derivative, which is then subjected to the action of iodine.

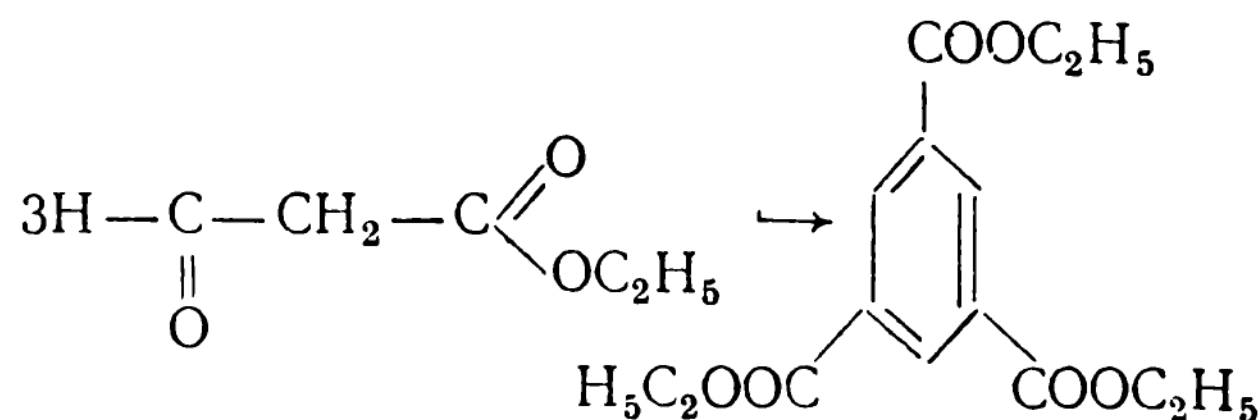
The thus obtained diethyl α , α' -dicarbethoxysuccinate has two hydrogen atoms, which can easily be removed as a proton, and also contains two carbethoxy groups for each of the two carbon atoms. All this permits using the ester in question in the same reactions as malonic ester (C-alkylation, saponification with decarboxylation).

57. Benzoylacetone can be produced by condensation of acetone with ethyl benzoate or of acetophenone with ethyl acetate by the action of sodium ethoxide. Benzoylacetone is capable of displaying keto-enol tautomerism and its properties resemble those of acetylacetone.

58. Though the pathway "a" involves only one step, a synthesis carried out in two steps (the route "b") is to be preferred since both the C-benzoylation of sodioacetoacetic ester and its subsequent cleavage lead to good yields.

When a mixture of ethyl benzoate and ethyl acetate is treated with sodium ethylate (the route "a"), the ethyl acetate undergoes self-condensation, yielding acetoacetic ester. The resulting mixture, in which acetoacetic, rather than benzoylacetic, ester predominates, cannot be separated so easily as it might be expected.

59. The sodium derivative of formylacetic ester is prepared by treatment of a mixture of ethyl formate and ethyl acetate with sodium. The ester itself cannot be isolated in pure form since it immediately undergoes self-condensation, as a result of which trimesic ester is formed (see answers 42 and 46).



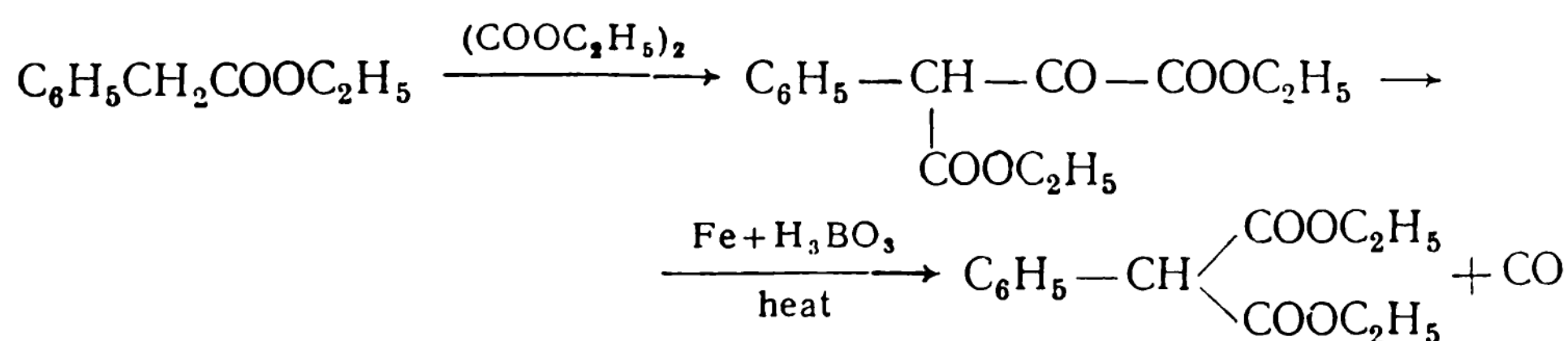
60. Acetoneoxalic ester, $\text{CH}_3-\text{CO}-\text{CH}_2-\text{CO}-\text{COOC}_2\text{H}_5$, is produced by condensation of acetone with diethyl oxalate through the action of sodium ethoxide. It shows keto-enol tautomerism.

61. Ethyl phenylacetate when subjected to the action of sodium ethoxide enters into an ester condensation with formation of ethyl 2,4-diphenyl-3-ketobutyrates.

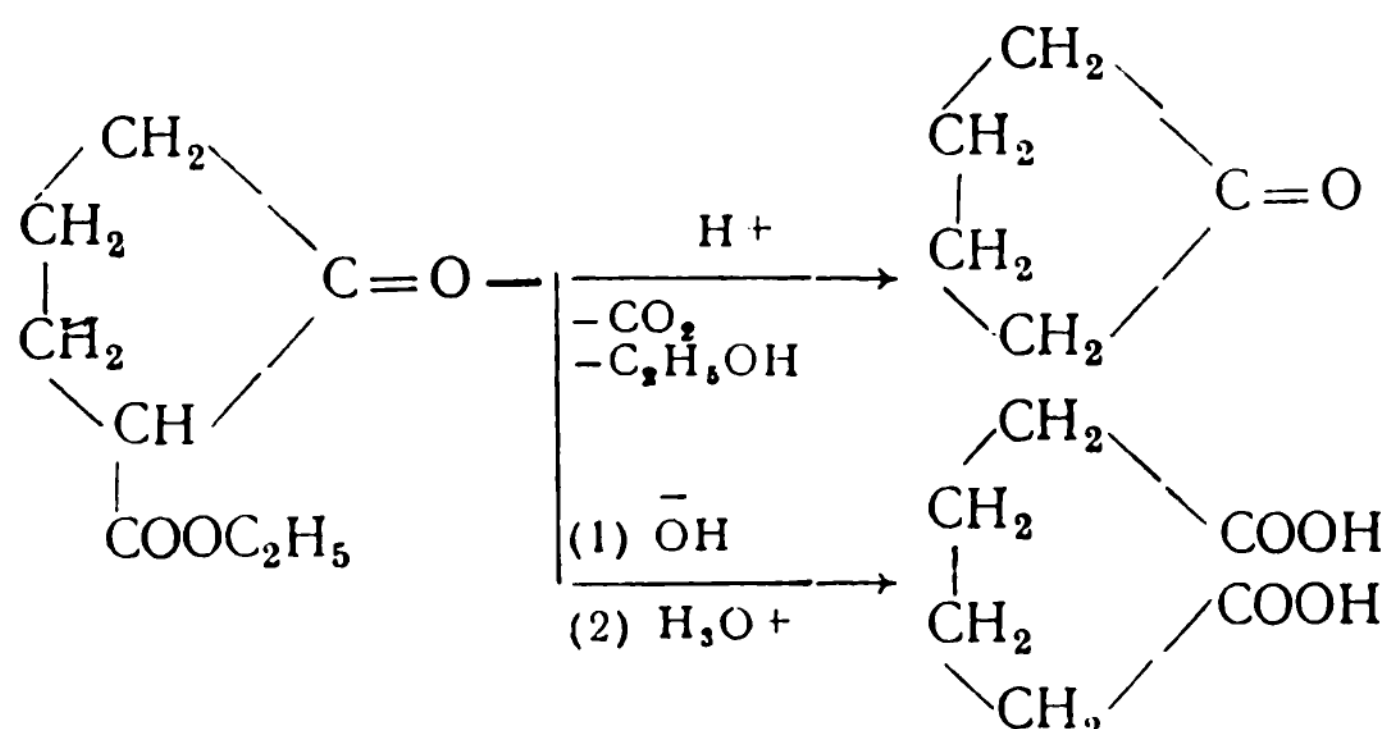
62. Phenylacetic acid is converted to dibenzyl ketone by catalytic ketonization (over manganous oxide or thorium oxide at 350-420°C). Benzaldehyde is converted to benzoin and the latter is oxidized to benzyl, $\text{C}_6\text{H}_5\text{—CO—CO—C}_6\text{H}_5$. The condensation of dibenzyl ketone and benzyl in an alkaline medium gives 2,3,4,5-tetraphenylcyclopentadienone.

63. Diethyl phenylmalonate cannot be obtained via sodiomalonic ester since the latter cannot be condensed with poorly reactive benzene halide. The compound in question is produced by condensation of ethyl phenylacetate with diethyl carbonate.

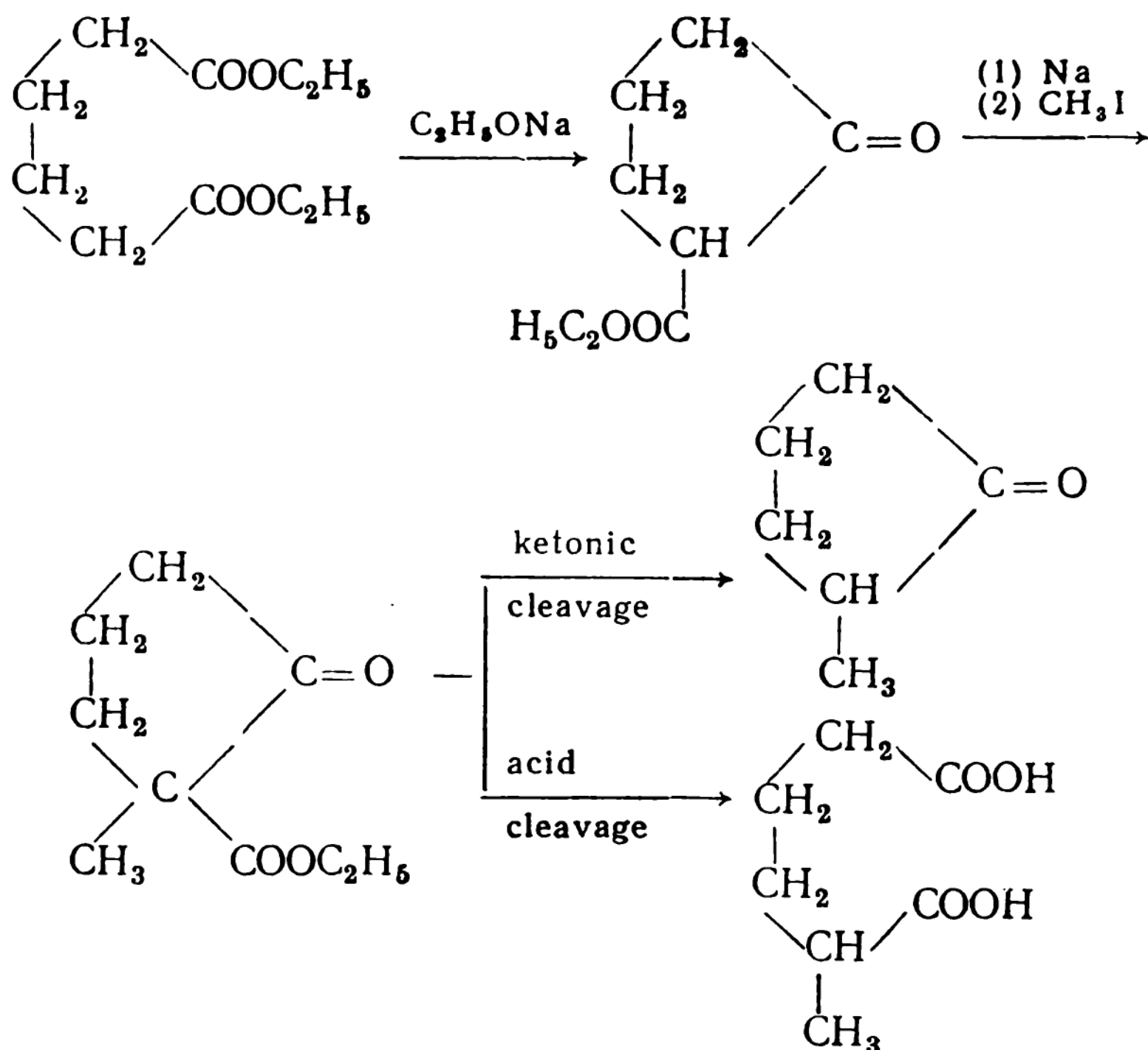
In practice, the best results are provided by the condensation of ethyl phenylacetate with diethyl oxalate followed by decarbonylation:



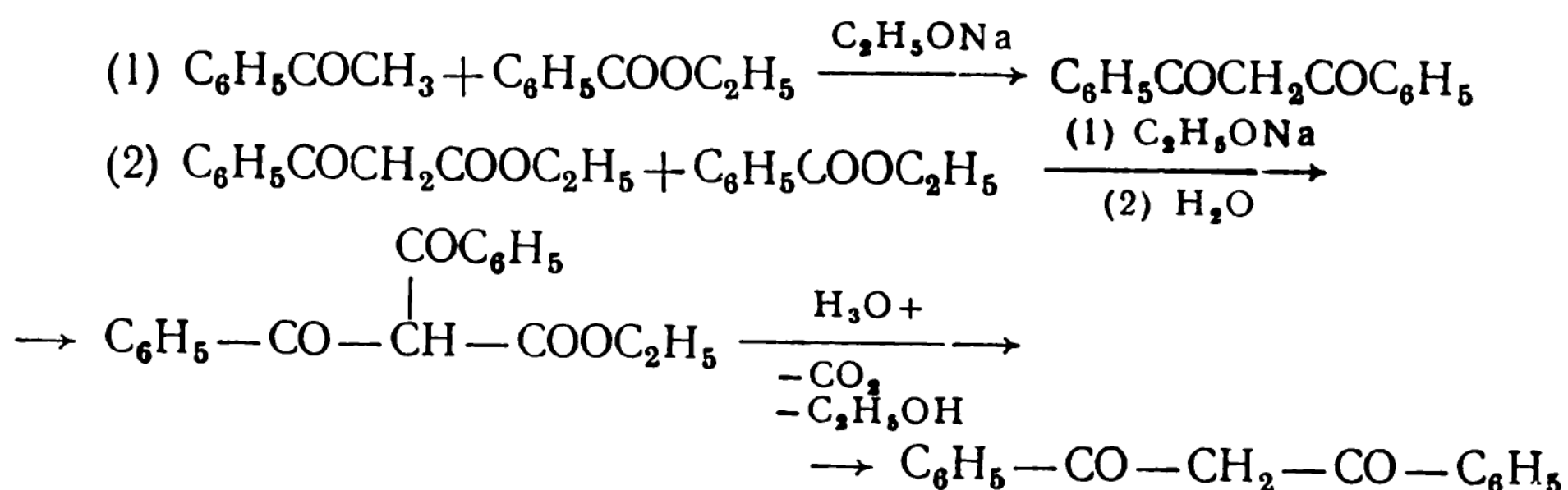
64. The intramolecular ester condensation results in α -carbethoxycyclopentanone. When subjected to alkaline and acid hydrolysis the compound formed reacts as follows:



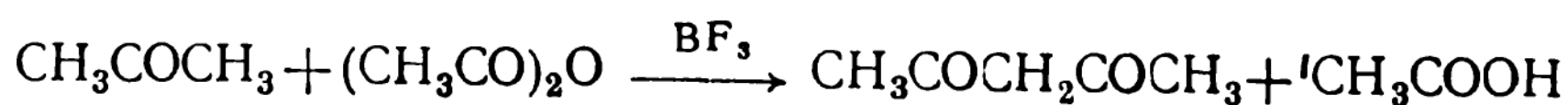
65.



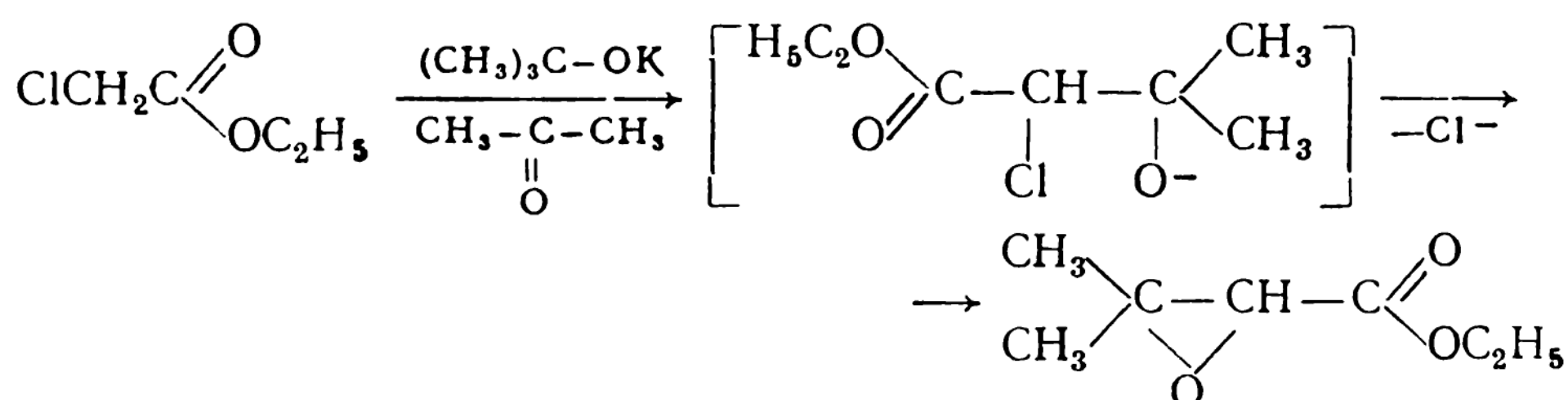
66. For dibenzoylmethane to be prepared use is made of two methods: the condensation of acetophenone with ethyl benzoate by the action of sodium ethoxide or the synthesis using benzoylacetic ester:



Acetylacetone is obtained by the condensation of acetone with ethyl acetate under the action of sodium ethoxide, or of acetone and acetic anhydride by the action of boron trifluoride:



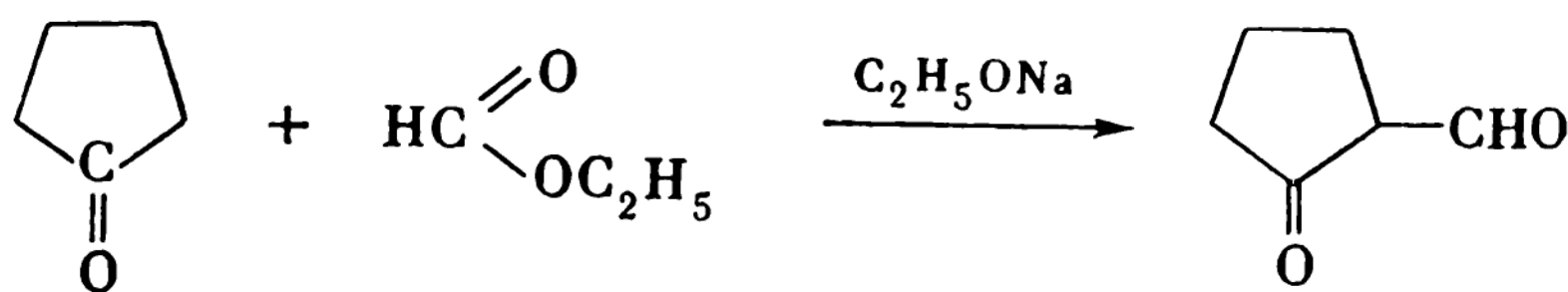
67. If the esters of α -halogen acids or α -halogen ketones are used as the methylene component in the condensation with ketones, the aldol formed as an intermediate in the reaction undergoes cyclization with formation of the corresponding α -oxide (Darzens reaction), for example,



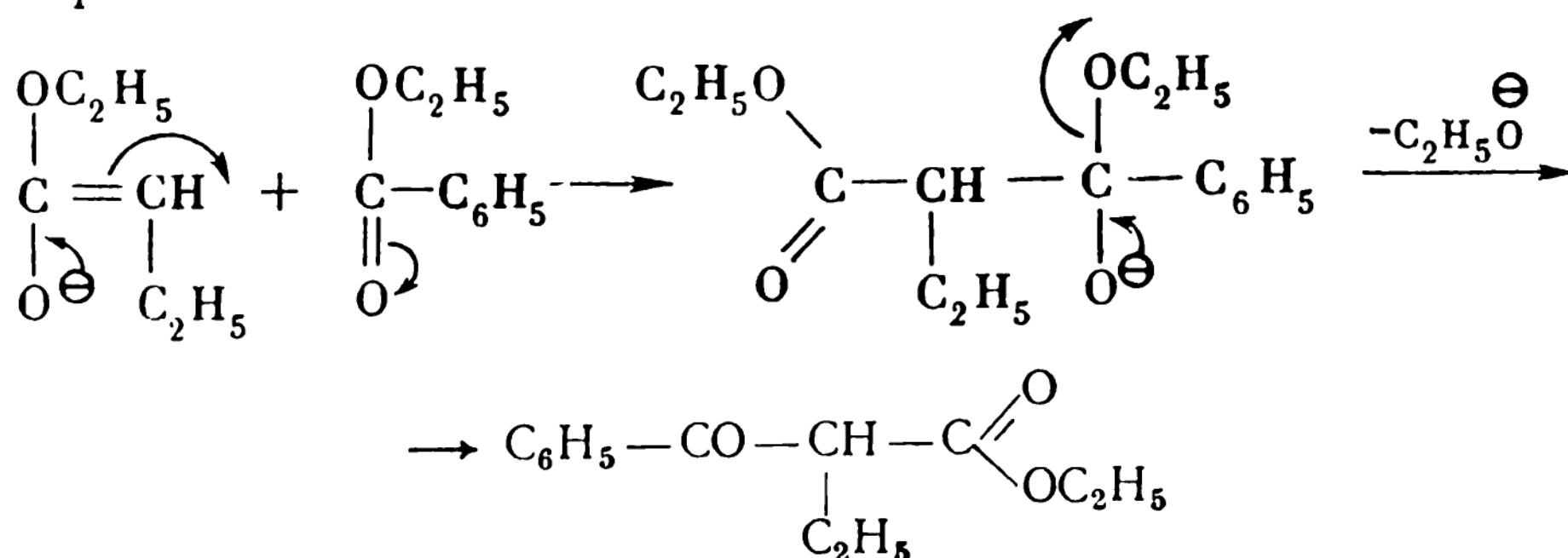
Since the condensing agents are strong bases, aliphatic aldehydes cannot be used as the carbonyl component (to avoid polymerization).

68. An example of the Darzens reaction—see the previous answer.

69.



70. The action of sodium amide results in the removal of a proton from the alpha-position in ethylbutyrate, the anion formed adds to ethyl benzoate, and then the ethoxide anion is split off:



This process leads also to the formation of a certain amount of the product of self-condensation of ethyl butyrate.

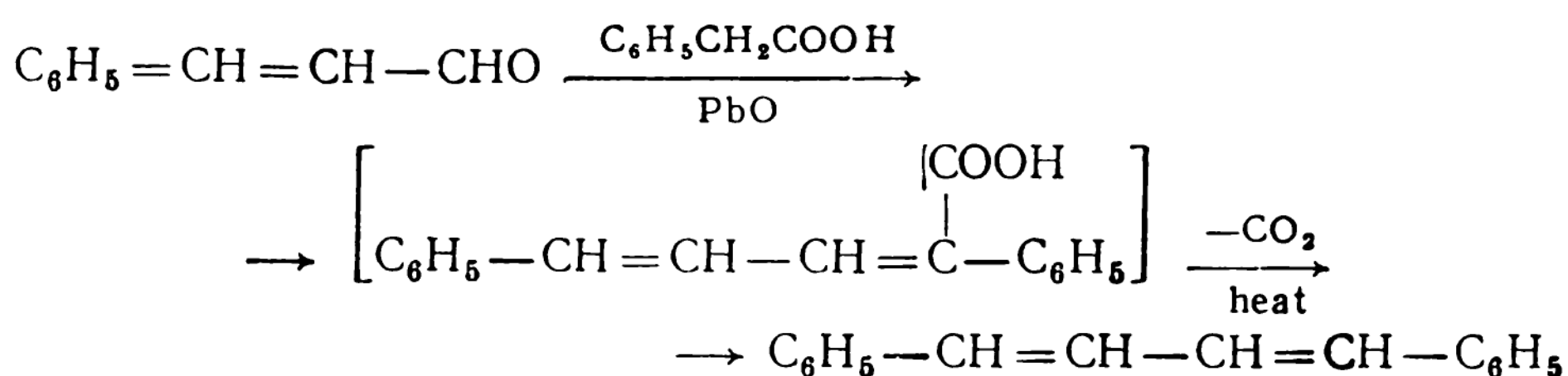
71. (a) From benzaldehyde and acetic anhydride by the Perkin condensation.

(b) By the croton condensation of acetaldehyde and acetone.

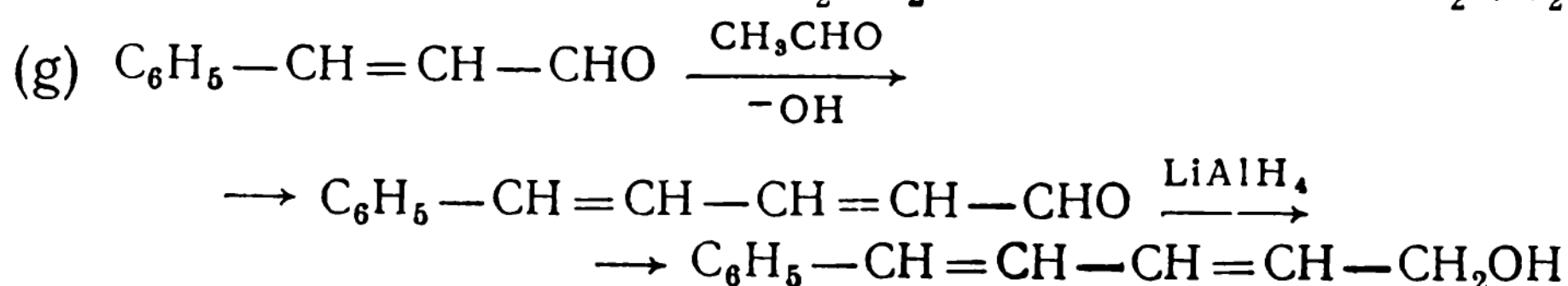
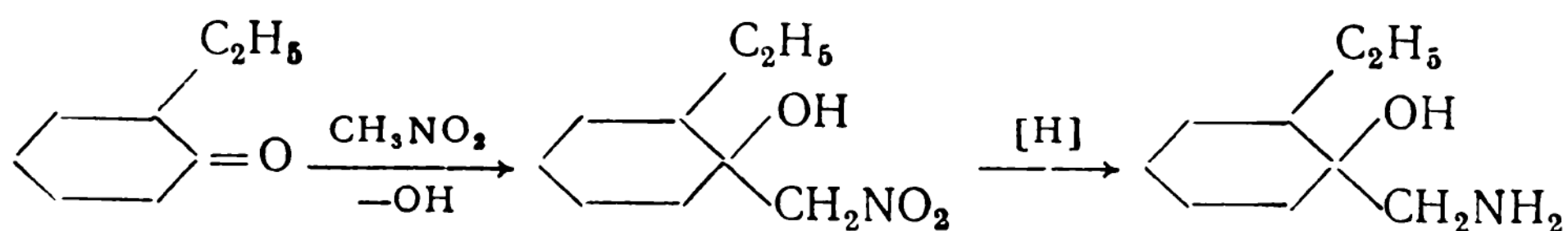
(c) By the catalytic hydrogenation of benzalacetone prepared by the condensation of benzaldehyde and acetone.

(d) Malonic acid is subjected to condensation with cinnaldehyde (in the presence of pyridine); the dibasic acid formed is decarboxylated on heating.

(e) Cinnaldehyde is introduced into a croton-type condensation with phenylacetic acid (the condensing agent is PbO), and the resulting product is subjected to thermal decarboxylation:

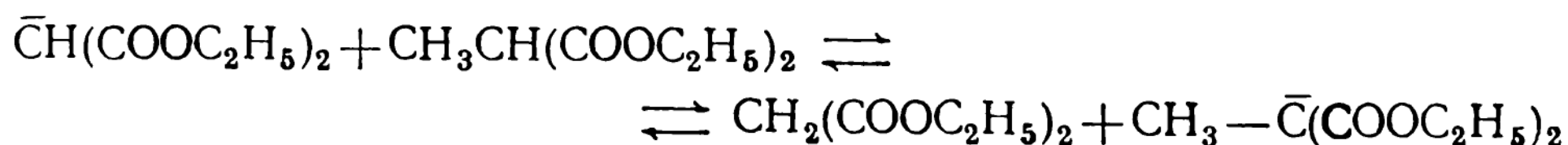


(f) Diethyl adipate is subjected to a ring-forming reaction (the Dieckmann cyclization) and the alkylation with ethyl iodide and ketonic cleavage are carried out (see answer 65); then the following reactions are accomplished:



(h) The condensation of benzaldehyde with phenylacetic acid is carried out and the unsaturated acid obtained is decarboxylated by heating in quinoline in the presence of powdered copper.

72. In the course of alkylation, in the reaction mixture there is established an equilibrium between the yet unreacted anion of malonic acid and the methylmalonic ester formed:



79. Sodiaoacetoacetic ester is subjected to the action of: (a) benzyl chloride; (b) ethyl β -bromopropionate; and (c) iodine. The resulting substituted acetoacetic esters are hydrolysed and decarboxylated by heating with dilute mineral acid.

80. 3-Isopropylhexan-2-one.

81. (a) The methyl and propyl radicals are successively introduced into a molecule of malonic ester. The resulting ester is saponified and the substituted malonic acid is decarboxylated by heating.

(b) The synthesis is effected via dimethylmalonic or dimethylacetoacetic esters.

(c) Sodiomalonic ester is treated with iodine, the resulting ester of ethanetetra-carboxylic acid is saponified, and the acid is decarboxylated by heating.

(d) It is obtained from sodiaoacetoacetic ester and isobutyl bromide with subsequent ketonic cleavage.

(e) When acetoacetic ester is heated with acetyl chloride and magnesium, ethyl diacetoacetate results.

When hydrolysed by dilute sulphuric acid the ester is saponified and decarboxylated to give acetylacetone.

(f) See answer 79c.

(g) In the same way as acetonylacetone is produced (see answer 79c) but from methylacetoacetic ester.

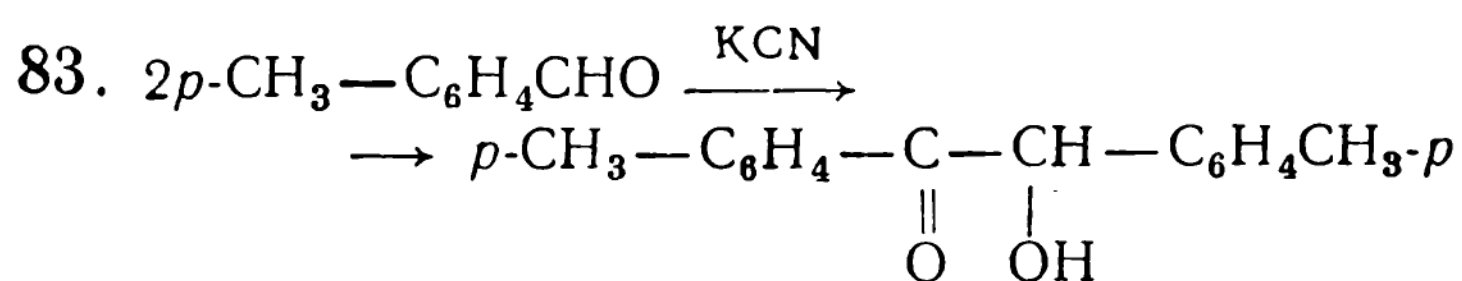
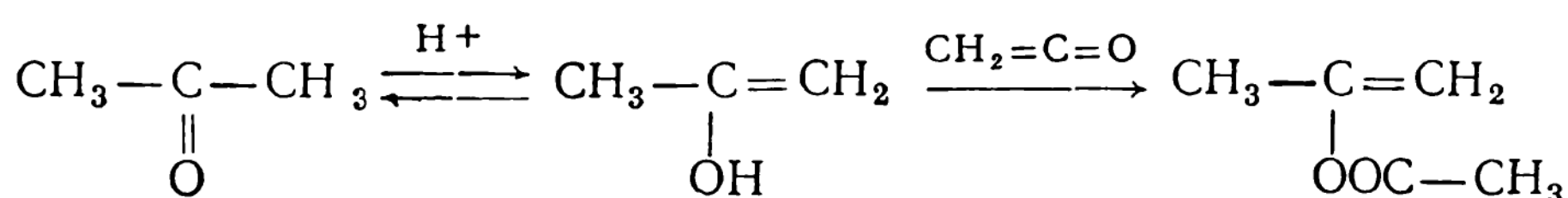
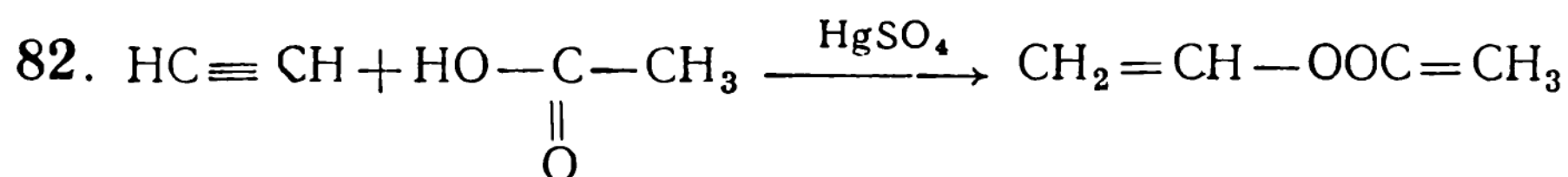
(h) First, isopropylacetoacetic ester is prepared from sodiaoacetoacetic ester and isopropyl bromide. Then its sodium derivative is "cross-linked" by the action of iodine and ketonic cleavage (decarboxylation by heating with dilute acid) is effected.

(i) Sodiaoacetoacetic ester is treated with iodine, and the diacetylsuccinic ester obtained is converted into a monosodium derivative and then alkylated with ethyl iodide or bromide; the final step is acid cleavage.

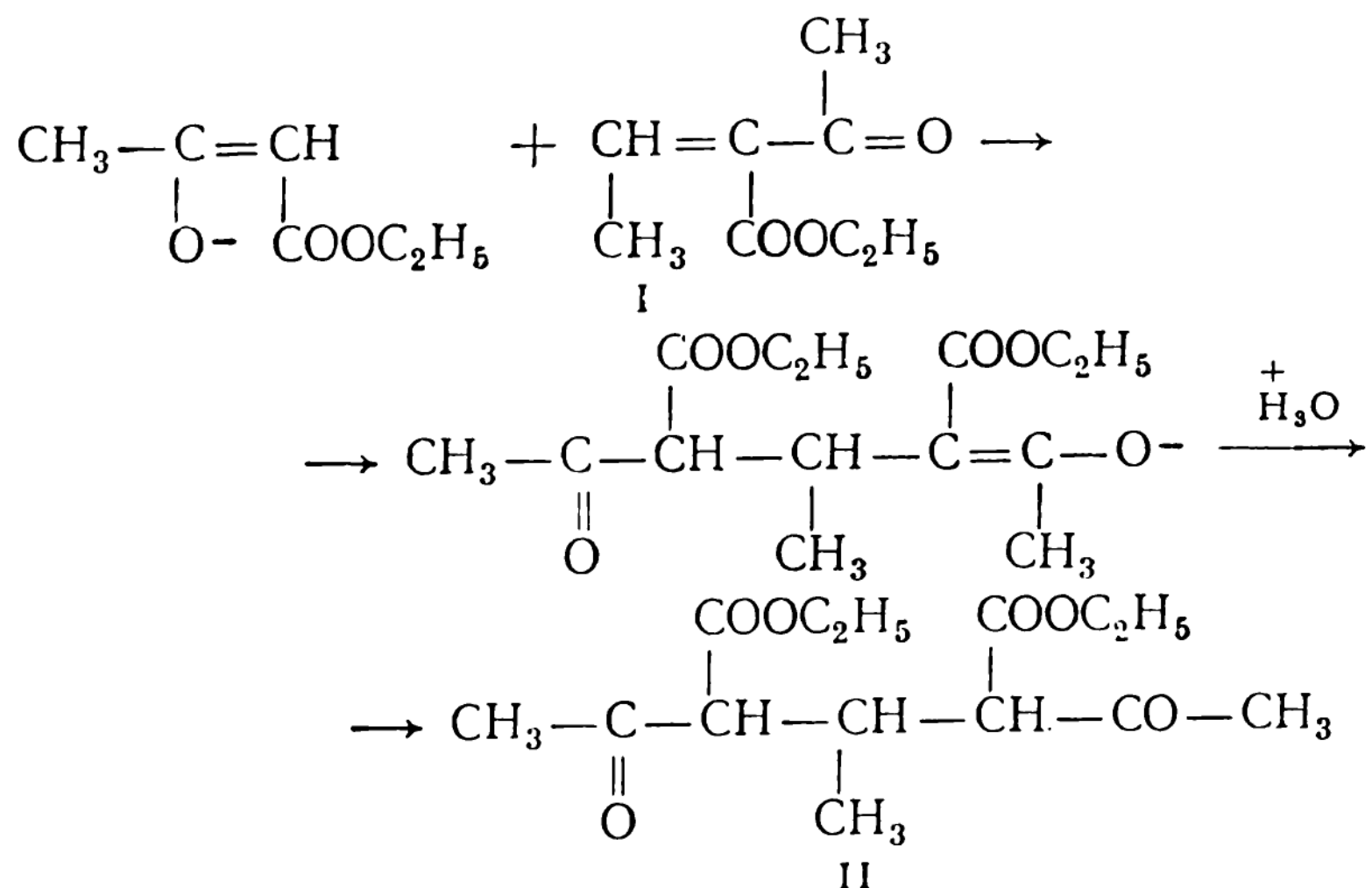
(j) Sodiaoacetoacetic ester is alkylated with methyl iodide; then methyl ethyl ketone is prepared by ketonic cleavage of methylacetoacetic ester. Ethylene ketal is synthesized by heating methyl ethyl ketone with dry glycol in the presence of catalytic amounts of *p*-toluenesulphonic acid.

(k) Methylmalonic ester is subjected to condensation with bromoacetone, and the resulting compound is saponified

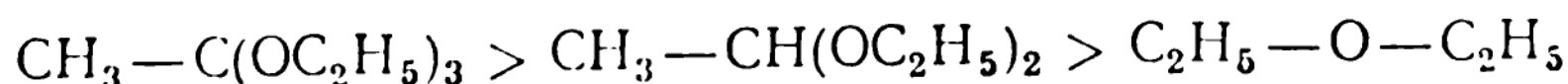
and decarboxylated to give α -methyl-levulinic acid.



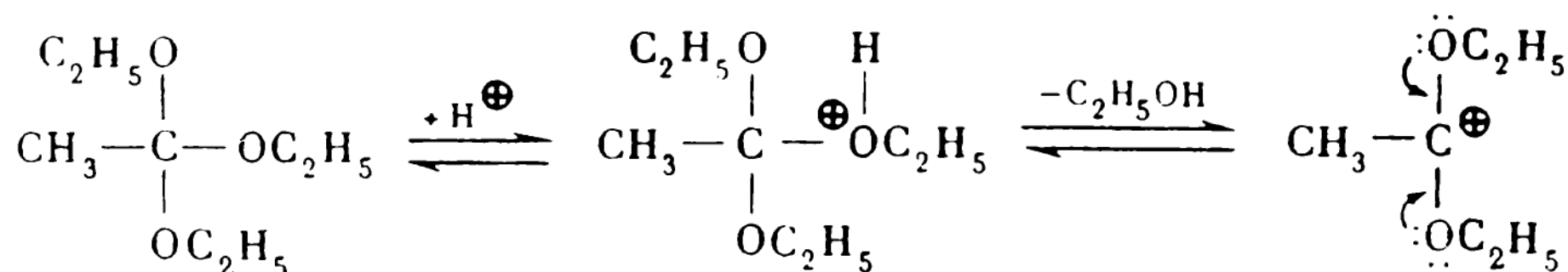
84. Ethylideneacetoacetic ester (I) results from the condensation of acetaldehyde (the carbonyl component) and acetoacetic ester (the methylene component) in the presence of piperidine or diethylamine. Then the enolate anion of acetoacetic ester adds on to the compound (I) and, as a result, ethylidene-bis-acetoacetic ester (II) is formed:



85. The rate of acid cleavage varies as follows:



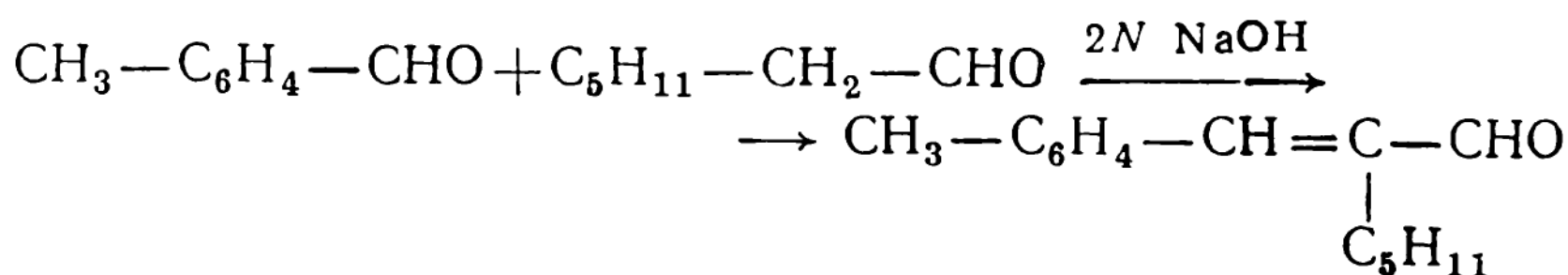
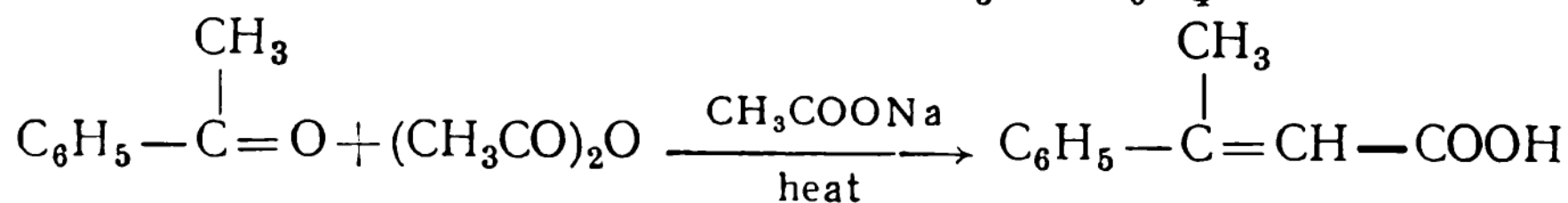
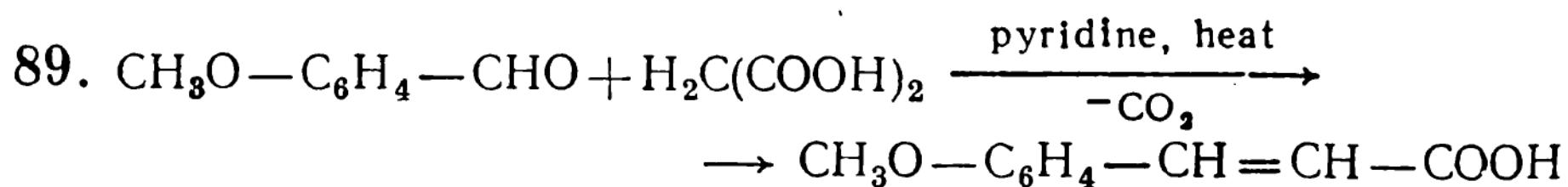
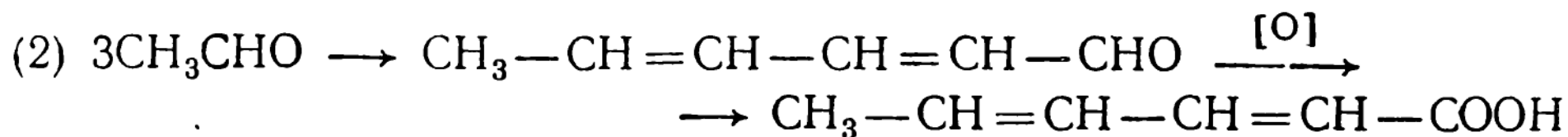
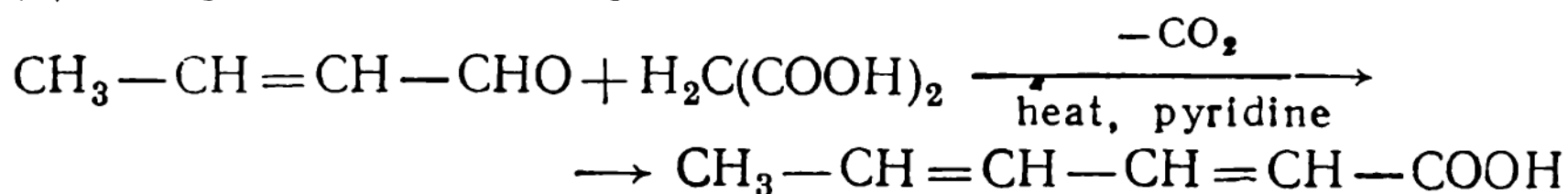
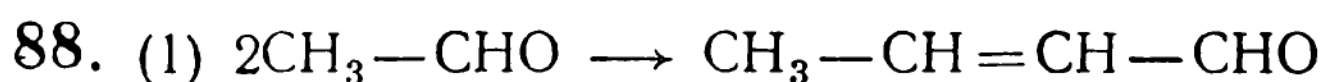
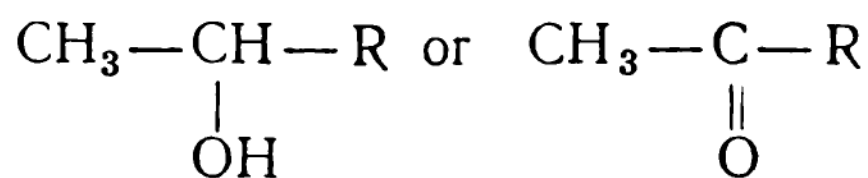
This order of variation is related to the stability of the carbonium ions formed during the process:

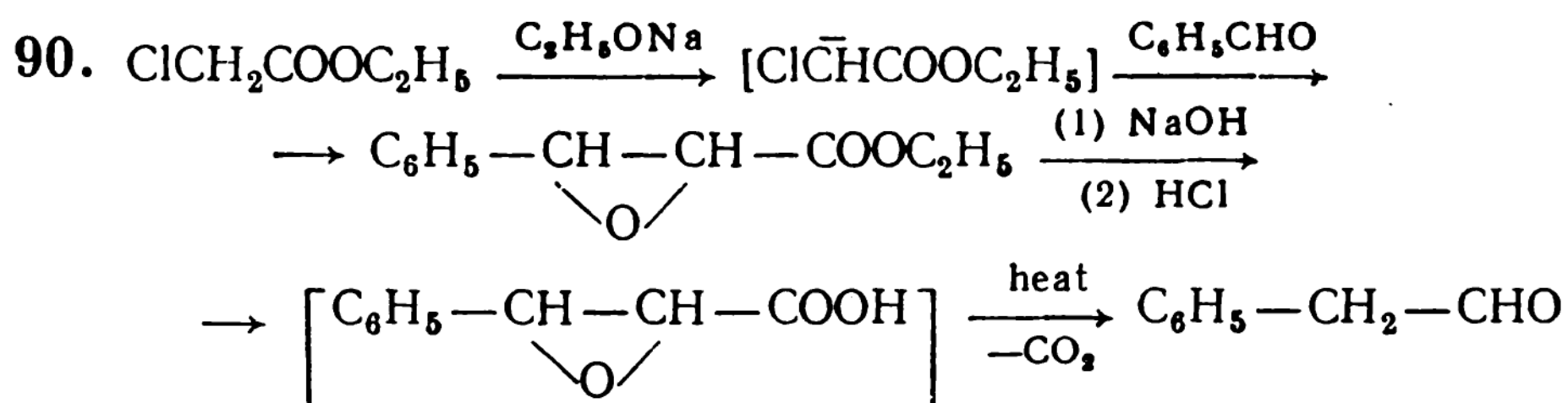


The increase of the number of alkoxy substituents at the carbonium-ion centre contributes to the ease of formation of the corresponding carbonium ion due to the mesomeric effect of the alkoxy groups (partial suppression of the positive charge on the carbon atom).

86. It is only 1,1- and 2,2-dimethoxypropanes that will be readily hydrolysed in an acidic medium. The hydrolysis of the former yields propionaldehyde, which can be detected by the silver mirror reaction, and that of the latter gives acetone, which can be identified by the preparation of its derivatives (2,4-dinitrophenylhydrazone, oxime, etc.).

87. The iodoform reaction is given by compounds of the structure





(see also answers 67 and 68).

91. In the same way as above, with the only difference that acetophenone is used instead of benzaldehyde.

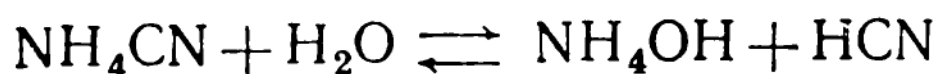
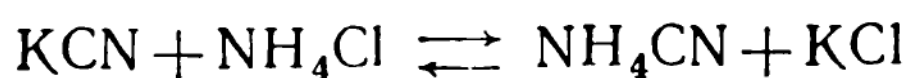
92. (a) By condensation of ethyl phenyl ketone and acetylene by the action of alkali.

(b) By organomagnesium synthesis from cyclohexanone and ethylmagnesium bromide.

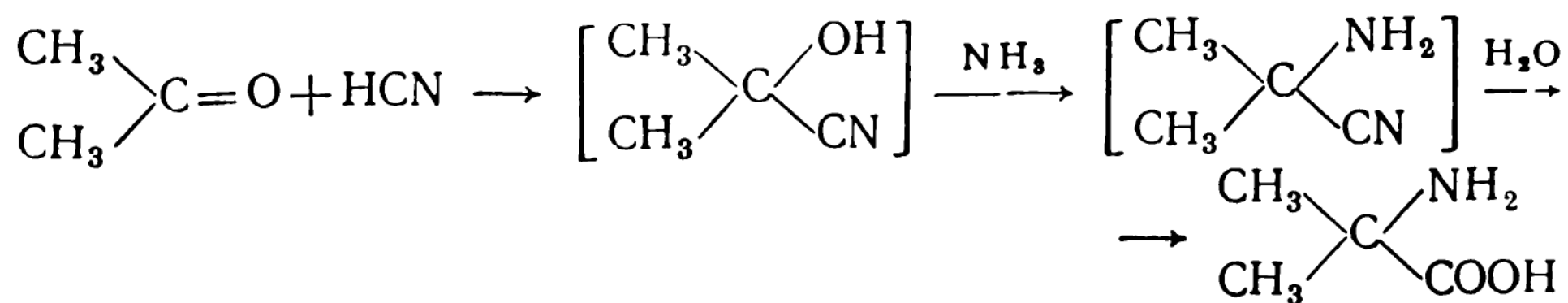
(c) By the action of acetaldehyde on $\text{IMg}-\text{C}\equiv\text{C}-\text{MgI}$

93. The substance belongs to ketals, which are stable in an alkaline medium and are hydrolysable by the action of acids.

94. An aqueous solution of a mixture of potassium cyanide and ammonium chloride is taken:



and acetone is added to it

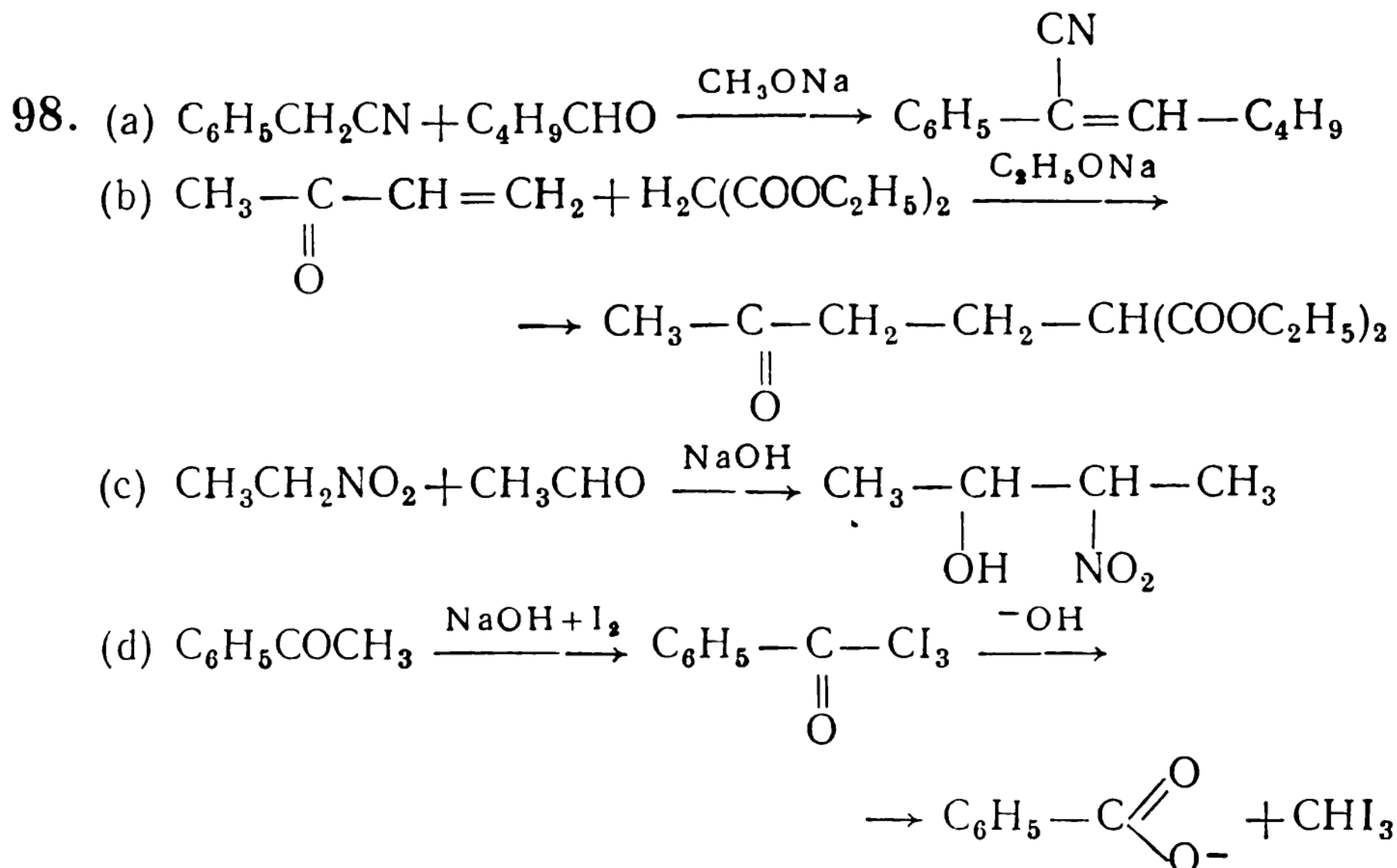


95. Cyanohydrin is to be obtained and saponified.

96. Readily decarboxylizable benzalmalonic acid.

97. In this case, for cyclic acyloin to be prepared from a diester, the reaction should be carried out in a large amount of boiling xylene in the presence of finely divided sodium in a current of nitrogen on rather vigorous mixing. In this way, conditions are created for an intramolecular process to be effected and the intermolecular condensation that would

lead to the formation of polymers is suppressed.



99. (a) Via cyanohydrin with subsequent hydrolysis.

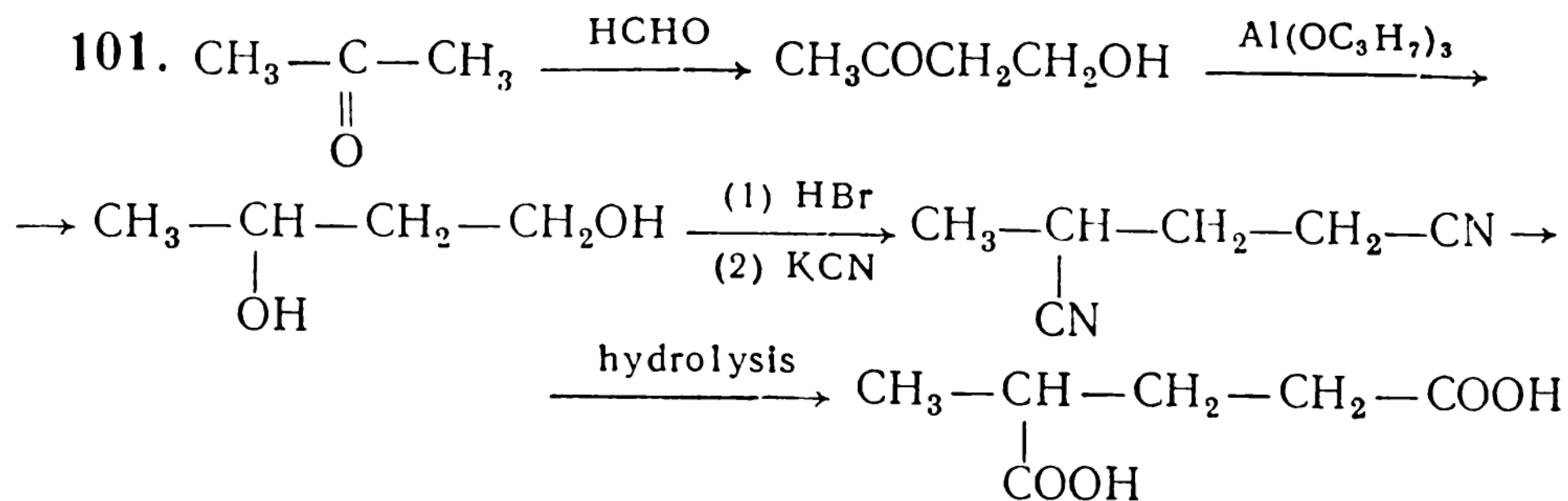
(b) By the action of ethylmagnesium bromide and subsequent hydrolysis.

(c) See answer 94.

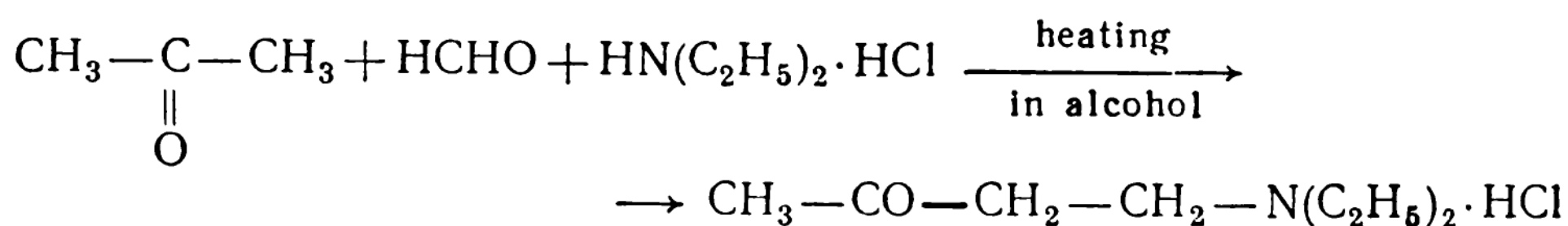
(d) By the condensation with malonic acid in the presence of pyridine with subsequent decarboxylation (heating) and esterification.

(e) By the reaction with hydrazine (preparation of azine).

100. In this reaction, benzaldehyde is the carbonyl component. The molecule of the methylene component must contain hydrogen atoms that are readily split off as protons. Acetic anhydride has such atoms (the electron-accepting effect of the anhydride grouping), whereas sodium acetate has not (it contains a negatively charged carboxylate-anion group).



102. By the use of the Mannich reaction



103. $\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{NC}_5\text{H}_{10}$.

104. 1-Dimethylamino-2-methylpentan-3-one.

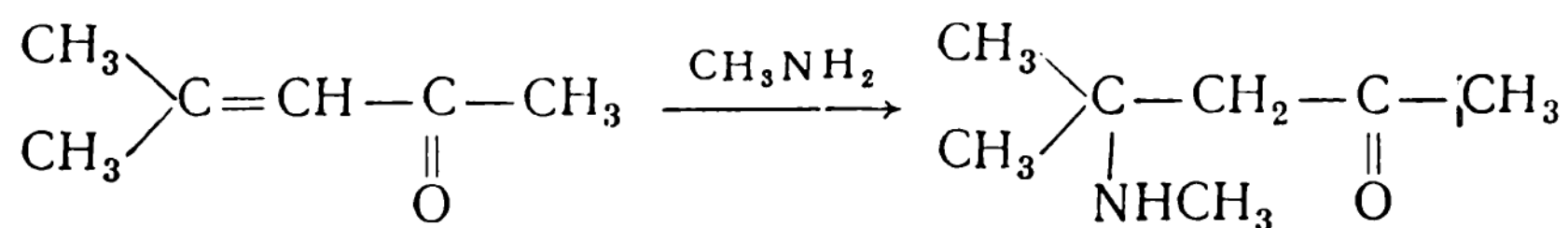
105. This is the formula of paraldehyde. It is resistant to the action of alkalis and can be cleaved by acids to form acetaldehyde. Paraldehyde is obtained by addition of traces of a strong mineral acid to acetaldehyde.

106. Steric hindrances.

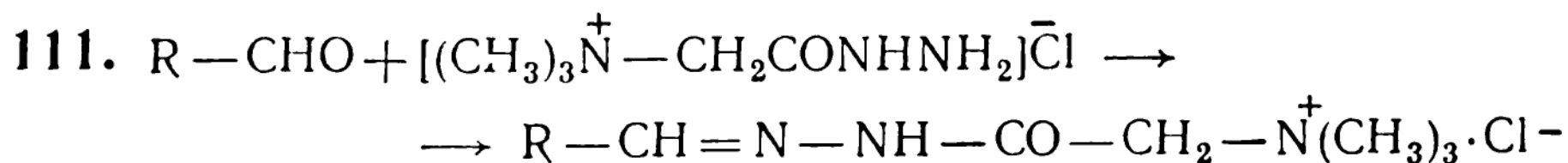
107. From pentaerythritol and cyclopentanone in the presence of catalytic amounts of arylsulphonic acid (for example, *p*-toluenesulphonic acid) with azeotropic distillation of water. Being an acetal, this substance is capable of being hydrolysed in acidic medium.

108. Acetone adds on (due to the mobility of the hydrogen of methyl groups in alkaline medium) to the ethylenic bond of acrylonitrile. There takes place what is called cyanoethylation. Depending on the reaction conditions, acetone can add from one to six molecules of acrylonitrile.

109.



110. By steric hindrances.



112. Through the effect of two carbethoxy groups: one of them is situated next to the CH_2 group, and the effect of the other is transmitted via the vinyl group.

CHAPTER 5

OXIDATION AND REDUCTION

INTRODUCTION

Oxidation and reduction reactions are conjugate processes and consist in the transfer of electrons from the reducing to the oxidizing agent. The change of the valency of elements in reactions of inorganic substances is easily followed and therefore the definition given above is very useful in classifying inorganic reactions.

For organic substances this definition is rather general—as a rule, there is no complete separation of charges in organic compounds and, in essence, any substitution reaction leading to the change of bond polarity in an organic compound may be regarded as an oxidation-reduction process (see, for example, Problem 3). For this reason, the concept of an oxidation-reduction process as the redistribution of electrons (addition of electrons to or their removal from the carbon atom or the molecule as a whole) is of no great importance to students studying organic chemistry and, besides, it is inconvenient for classifying reactions¹. It is more convenient to define oxidation as the enrichment of a substance in oxygen or the impoverishment in hydrogen; conversely, the enrichment in hydrogen or loss of oxygen is looked upon as the process of reduction.

The variety of reagents available and also the specificity of their action complicates the study of the processes of oxidation and reduction of organic compounds.

In order to be ready for solving problems one should compile several tables (separately for reduction and oxidation). One of these (intended for remembering the action of reducing and oxidizing agents) should be drawn up as follows:

¹ An important exception is the oxidation of the aromatic to the quinoid nucleus.

TABLE 1

Reducing agent	Substance to be reduced	Reaction product
Na/moist ether	Ketones	Secondary alcohols (the by-products are pinacols)
Na/NH ₃ (liquid)	Acetylenic hydrocarbons	Olefins
Na + ROH	Esters	Primary alcohols
LiAlH ₄	Aldehydes, ketones, acids, esters	Alcohols

The final result in these reactions depends, as a rule, on the entire oxidation-reduction (redox) system, i.e., not only on the reducing agent but also on the nature of the substance being reduced and the medium; it is therefore reasonable in certain cases to indicate in more detail the conditions of the reaction and the type of the substance to be reduced, for example,

Zn + acetic acid (or hydrochloric acid)	Aldehydes (enantiol)	Alcohols
Zn + hydrochloric acid	Aromatic ketones (benzophenone)	Pinacol
Zn/Hg + hydrochloric acid	Carbonyl in aldehydes, ketones	—CH ₂ — (Clemmensen reduction)

It is also useful to draw up tables, taking, as a basis, the class of the substance to be prepared (see Table 2) or of the starting material (see Table 3).

One may also compile a list of name reactions for oxidation and reduction, using the book by A. R. Surrey, *Name Reactions in Organic Chemistry*, Academic Press, New York and London, 1961.

Information necessary for compiling tables can be found in textbooks of organic chemistry: A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*.

TABLE 2

Class of compound being prepared	Class of initial substance	Reagent
Primary alcohols	Aldehydes Acids Esters	H_2/Pt ; metal + acid; $LiAlH_4$ $LiAlH_4$ Na/alcohol; $LiAlH_4$

TABLE 3

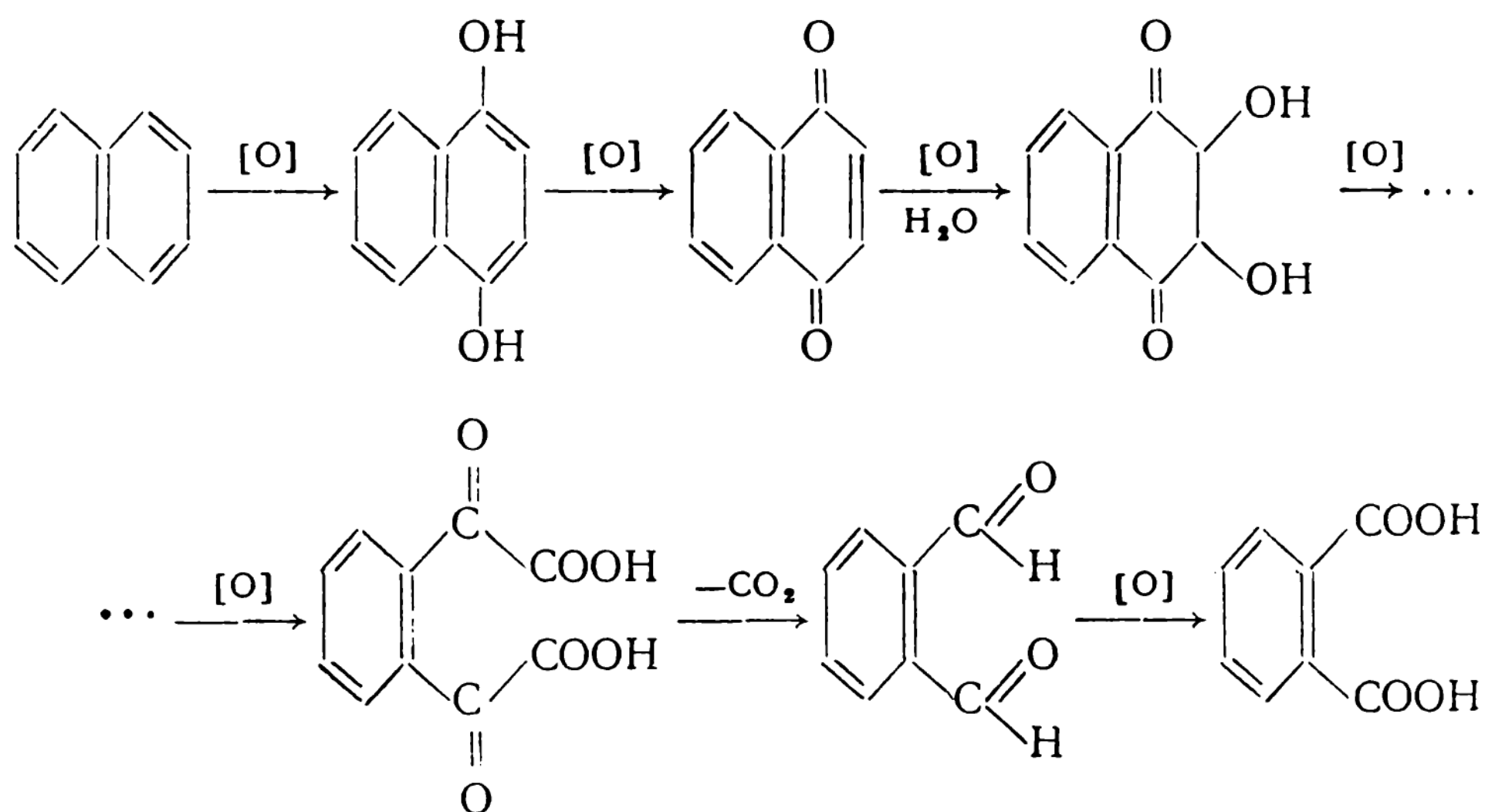
Class of starting substance	Reagent	Class of substance being prepared
Ketones	$Zn/Hg + HCl$ Mg/Hg , Al/Hg (in the absence of protons)	Hydrocarbons Pinacols

Khimiya, Moscow, 1969; J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965; D. J. Cram and G. S. Hammond, *Organic Chemistry*, 2nd ed., McGraw-Hill, 1964; R. C. Fuson, *Reactions of Organic Compounds*, 1962.

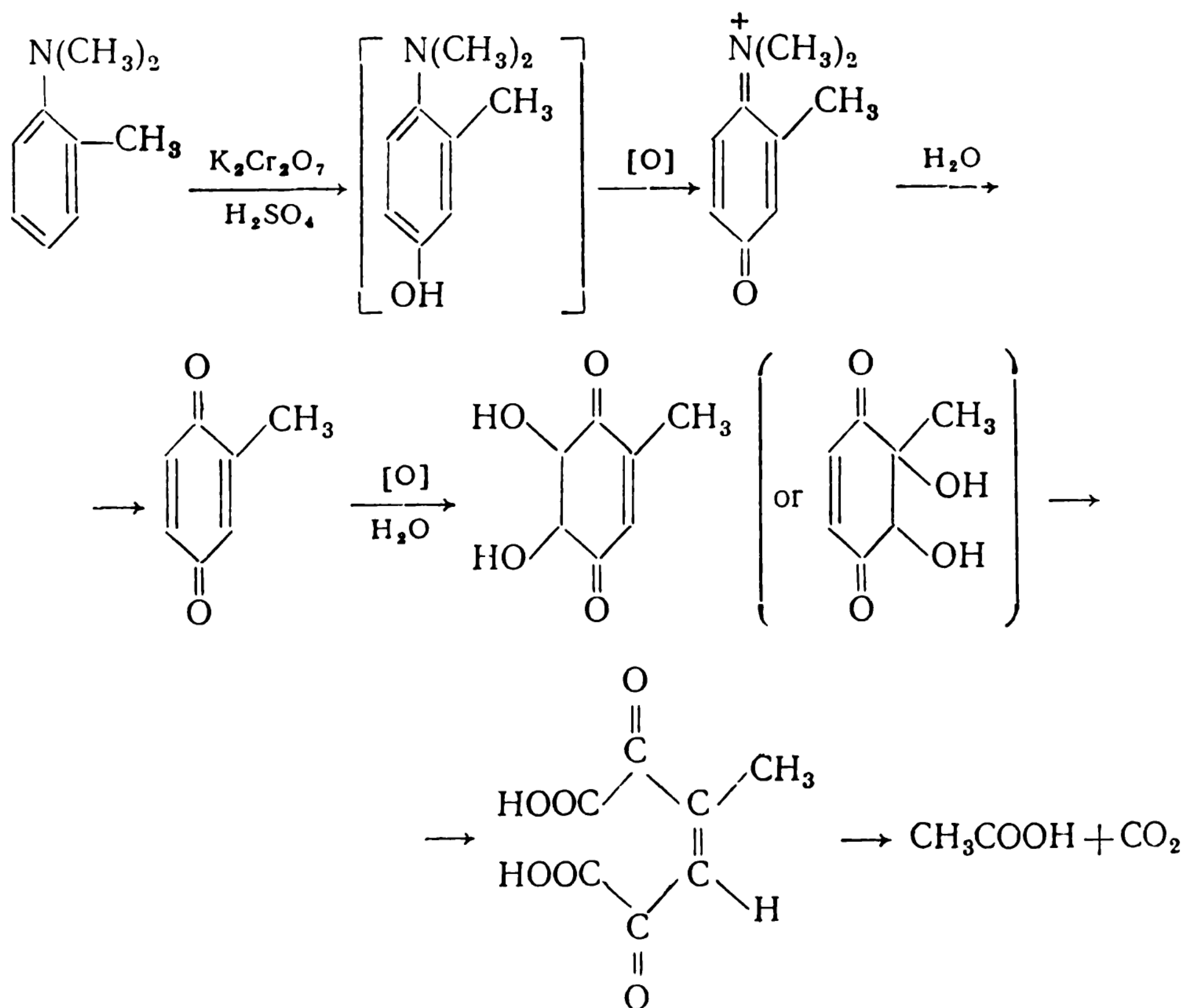
For a detailed study of oxidation-reduction reactions the reader is referred to W. A. Waters, *Mechanisms of Oxidation of Organic Compounds*, London-New York, 1964.

In studying reduction reactions it seems reasonable to pay attention to the similarity in the mechanisms associated with the hydride transfer (the Meerwein-Ponndorf-Verley reaction, the Oppenauer reaction, the Tishchenko reaction, the Cannizzaro reaction, the reduction of polar bonds by hydrides) and also to the difference between the reduction of carbonyl compounds in protic and aprotic media. In studying oxidation reactions it is often useful to consider the scheme, rather than the mechanism, of the successive oxidation of a substance, thereby choosing at each imaginable step of the reaction the most vulnerable point in the molecule

or the most labile bond, for example,



or



This method enables one to understand better the result of the reaction and to avoid errors. A typical error in the second example is the simultaneous oxidation of the nucleus and the methyl group (which would have resulted in the formation of $\text{O}=\text{C}_6\text{H}_4=\text{O}$); a step-by-step consideration of

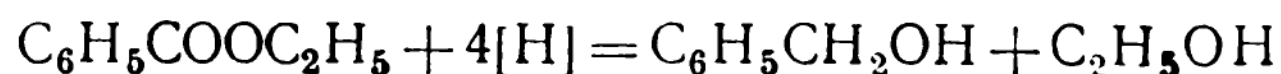
the reaction shows that intermediate compounds always contain groups that are more readily oxidized than the methyl group and therefore even under severe conditions it is only this group that remains unchanged.

For oxidation-reduction (redox) equations to be set up more quickly (Problems 7 and 21) it is useful to include in Table 1 the coefficients for those cases when lithium aluminium hydride or potassium permanganate is used. In a general case the coefficients for redox equations are chosen with the aid of the following equations:

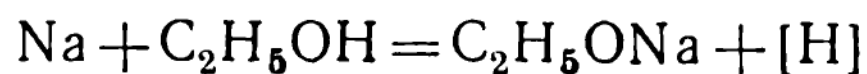
(1) The substance being reduced $+ [\text{H}] =$ reduction products;

(2) reducing agent $+ \text{H}_2\text{O} =$ products of oxidation of reducing agent $+ [\text{H}]$.

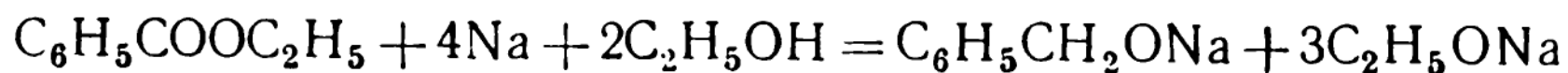
It is required, for example, to complete the equation and to choose coefficients for the case of the action of sodium and alcohol on ethyl benzoate. Using Table 3, we find that the reaction product is benzyl alcohol. We set up the first partial equation. The reaction products contain 4 hydrogen atoms more than the starting material, and therefore the $[\text{H}]$ must be preceded by the coefficient 4:



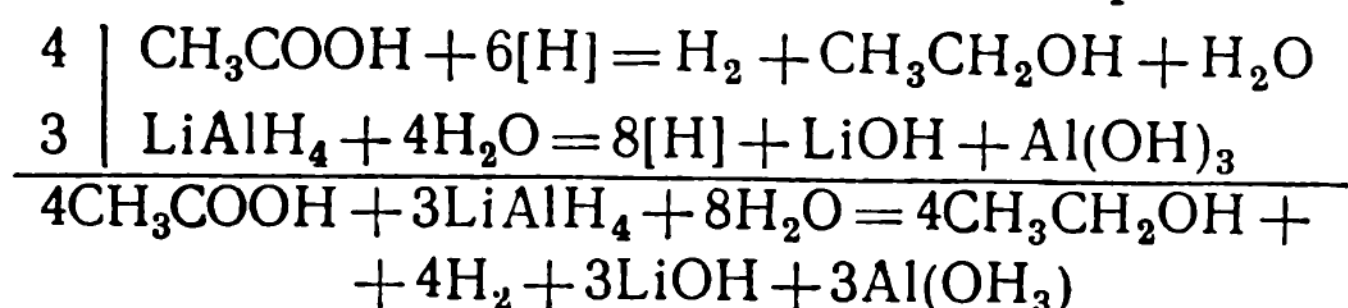
The second equation is



It is obvious that all the coefficients of the second equation must be multiplied by 4. In summing up these equations it should be taken into account that the reduction products in the first equation, benzyl and ethyl alcohols, react with sodium too. The sought-for overall equation is



If the process of conversion involves, apart from the reduction (or oxidation) of an organic substance, other reactions as well, they must also be taken into account in partial equations. For example, the reduction of acetic acid by lithium aluminium hydride to ethyl alcohol is accompanied by the evolution of hydrogen due to the reaction of lithium aluminium hydride with the mobile hydrogen of the acid, a fact that should be taken into account in the first partial equation:

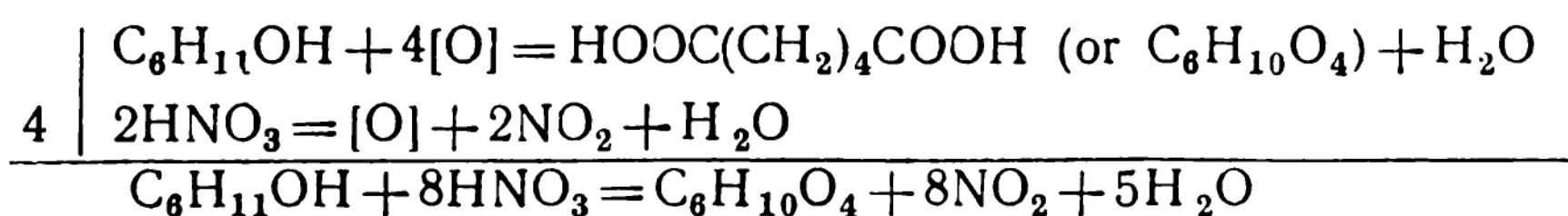


Equations for oxidation reactions are set up in the same way. In this case use is made of two equations having the following form:

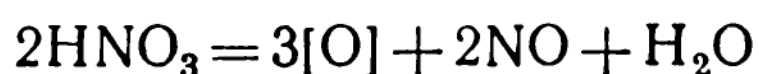
- (1) the substance being oxidized + [O] = oxidation products;
- (2) oxidizing agent + H₂O = [O] + products of reduction of oxidizing agent.

(In the latter equation water may be left out; it is often convenient to use a formal conception of a salt as a compound of two oxides, say, K₂O·2CrO₃ or K₂O·Mn₂O₇; this facilitates the setting-up of the equation.)

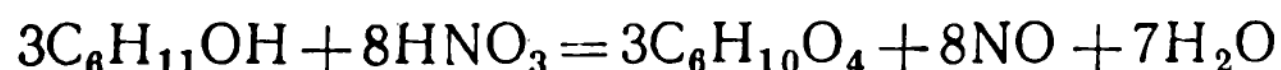
The equation for the oxidation of cyclohexanol by nitric acid, for example, can be conveniently written in the following form:



In choosing another equation for de-oxidation of nitric acid

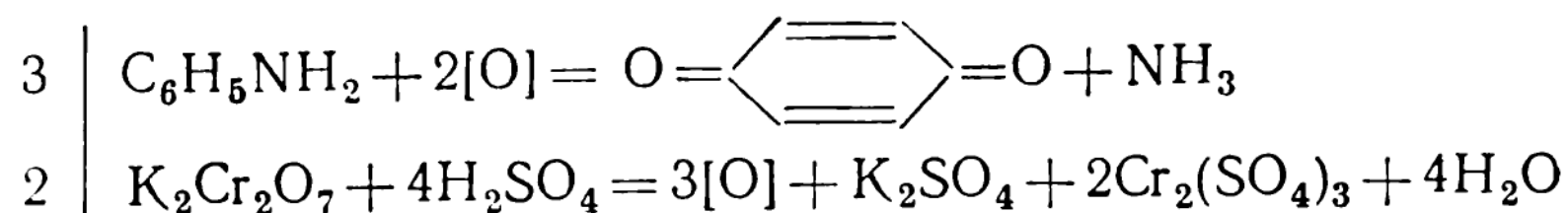


the coefficients of the overall equation will be different:

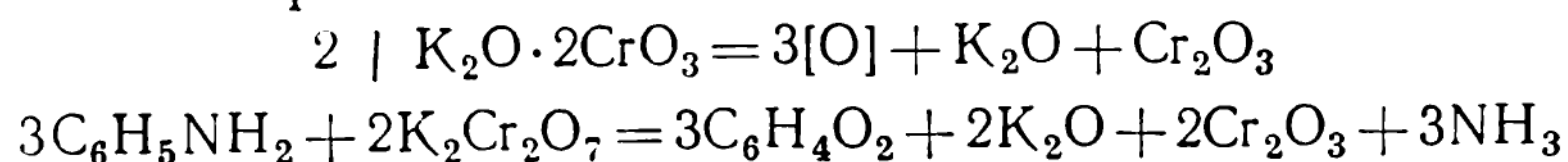


In practice, the reaction is carried out in such a way that the amount of nitric acid is not enough for the oxidation to proceed according to the first scheme and therefore there is formed a mixture of nitrogen oxides (when calculating the equation according to the second scheme there will naturally be a large excess of nitric acid).

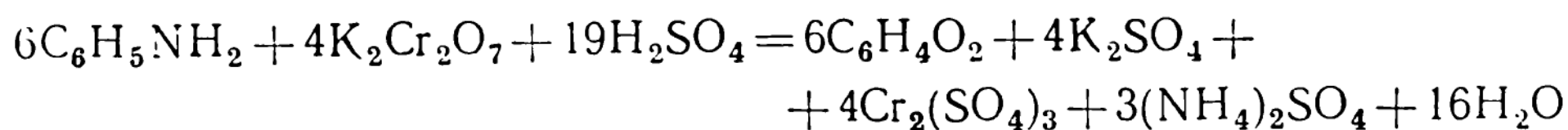
A more complex example is the setting-up of an equation for the oxidation of aniline to benzoquinone:



or a more simplified form:



We can then determine the amount of sulphuric acid required for the formation of salts. The overall equation will then assume the following form¹:



It should be emphasized that for equations to be set up it is not necessary to know the mechanism of the reactions or the scheme of conversions and even the structure of the compounds participating in the reaction; what is of importance here is the *composition of the starting materials and end products*. Using the data of Table 1 and the above-described methods of setting up equations, one can easily answer questions 7 and 21.

For Problems 12 and 23 to be solved one must know the relative ease of oxidation and reduction of various functional groups and the action of specific oxidizing and reducing agents (Table 1) and be able to apply various methods of protecting functional groups. This protection consists in preparing such a derivative that would be less sensitive to the action of certain reagents than the original functional group. It is important to keep in mind not only what types of protection of functional groups are used in carrying out oxidation-reduction reactions but also with respect to what reagents this protection is effective. One must not use, for example, acetal protection in the oxidation by the dichromate oxidizing mixture (acetals are readily hydrolysed in acidic solution); in this case one should use, as an oxidant,

¹ Since the oxidation of aniline proceeds in a very complicated way and is accompanied by side reactions, use is made in practice of a different molar ratio of aniline, potassium bichromate and sulphuric acid (0.25 : 0.235 : 2).

say, permanganate in a neutral or alkaline solution. A method of protection must be so chosen that, after the principal reaction is completed, the removal of the protecting groups should not change the new function formed as a result of the main, oxidation or reduction, reaction.

The examples from Problems 11 and 22 are to be solved with the aid of Tables 1 and 2, those from Problems 13 and 29 by the use of Tables 2 and 3; combination problems (39-44) are based on the material under "Oxidation and Reduction" with the use of other methods. In examples given in Problem 44 it is required that a comparison be made of the various synthetic techniques employed in organic chemistry to build up the carbon skeleton and to develop functional groups. For example, β -phenylethyl alcohol can be prepared by reduction of ethyl phenylacetate or phenylacetaldehyde with various reductants, by an organomagnesium synthesis, by the condensation of benzene with ethylene oxide, and by many other methods. Evidently, the reduction of phenylacetic aldehyde, which is usually made by the Darzens reaction, is the least favourable route because of the low availability of the starting material, while the reaction of phenylmagnesium bromide with ethylene oxide is a rather simple method. This reaction, however, involves the formation of α -phenylethyl alcohol as a by-product, which is difficult to separate by distillation, and for pure β -phenylethyl alcohol to be secured it may seem more convenient in certain cases to use the reduction of ethyl phenylacetate. Use should probably be made of lithium aluminium hydride as the reducing agent, which is a more convenient preparative technique and provides a higher yield of the product than the reduction by metallic sodium in ethyl alcohol (the Bouveault-Blanc reduction).

It is this comparative analysis of methods that will be of maximum use in solving the problems, and therefore some examples in Problem 44 should be used for recapitulating the course of organic chemistry.

Problems in structure determinations (45-60) involve the use of methods of oxidative degradation and of other methods as well. In dealing with problems that have no unique solution (49-53) one should know what additional information on the reactions involved has to be used (the ratio of the reaction

products, molecular weight, spectral characteristics, certain chemical properties) and by what methods these data could be obtained in practice.

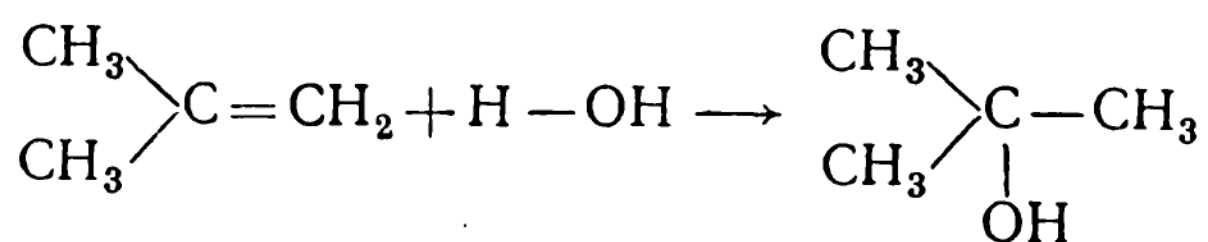
In solving problems on structure determination it is important to remember that the carbonyl and carboxyl groups appear in destruction products in place of easily oxidizable functional groups (alcoholic and aldehyde) and multiple bonds. Under more drastic conditions of oxidation ketones are also converted into a mixture of acids, this resulting, in the most general case, in the formation of four different acids. The lower number of acids formed in the oxidation of ketones or secondary alcohols can yield valuable data on the symmetry of the starting compound (see Problem 27). A consideration of the symmetry of the starting material will help solve Problems 47, 51, 57, and 58.

Problems and Exercises

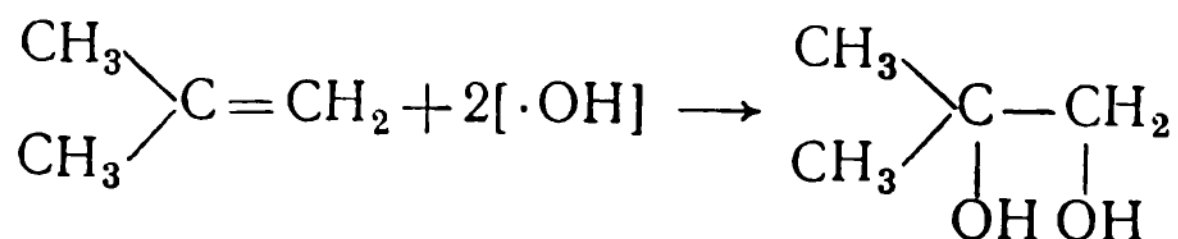
1. GENERAL QUESTIONS

1*. How are the following concepts related: tendency to oxidation and nucleophilicity or electrophilicity? What is the relation between the oxidizing action of reagents and their nucleophilicity or electrophilicity?

2. Compare the following two reactions

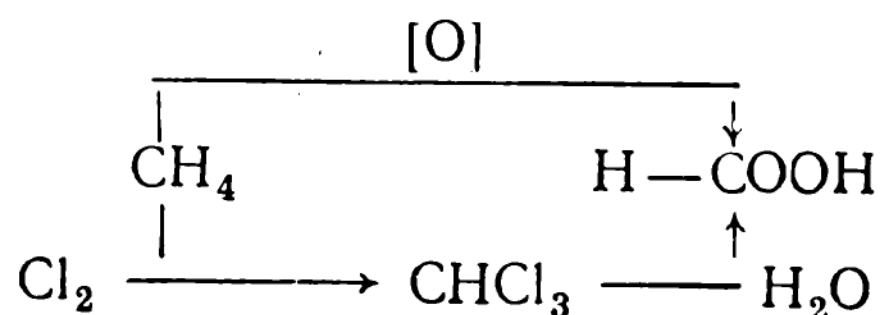


and



Which of these reactions is an oxidation reaction and why?

3. The conversion of methane to formic acid can basically be accomplished in two ways:



The upper route is explicitly an oxidation. When did it proceed in the lower scheme?

4. Consider the following scheme:



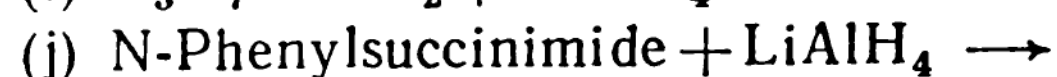
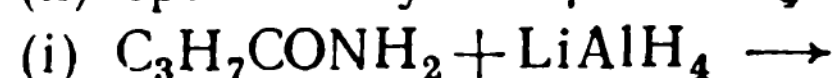
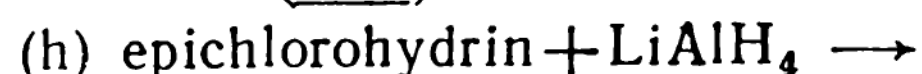
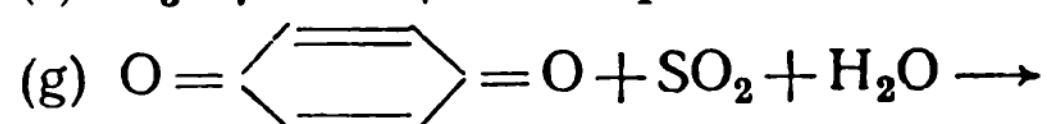
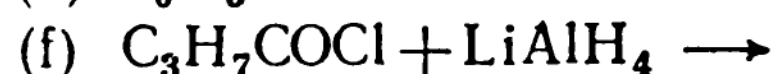
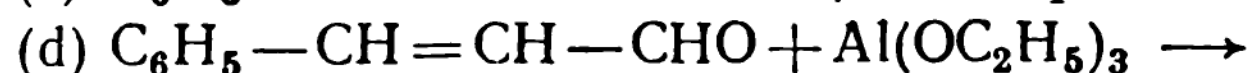
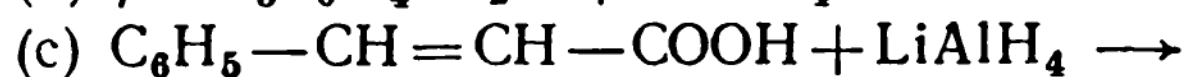
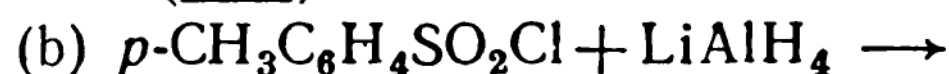
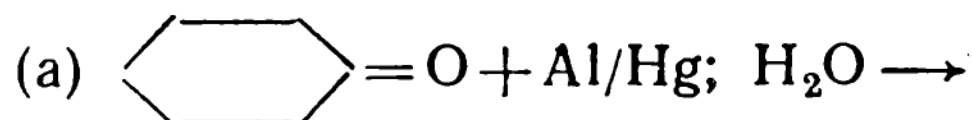
Oximes are derivatives of aldehydes and nitriles are derivatives of acids. What does the process of oxidation consist in?

5*. The preparation of aldehydes and ketones from acids is a reduction process. What compound is used as the reducing agent in the preparation of ketones by dry distillation of the calcium salts of acids?

6. What is the relation between the oxidation-reduction action and the normal redox potential of a system? How are these potentials determined?

2. REDUCTION

7. Complete the equations for the following reactions and balance them:



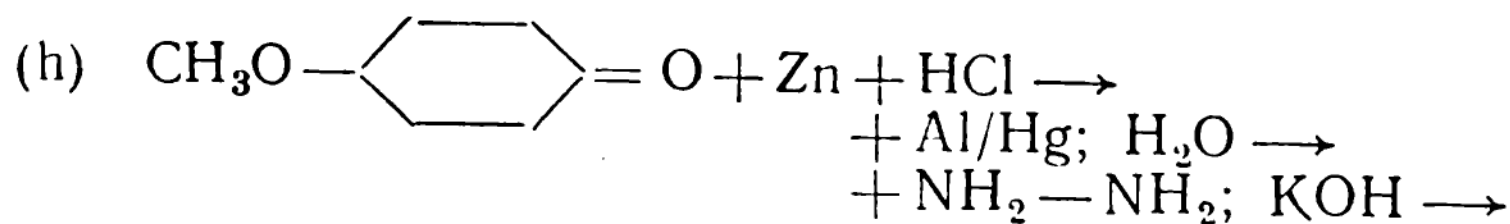
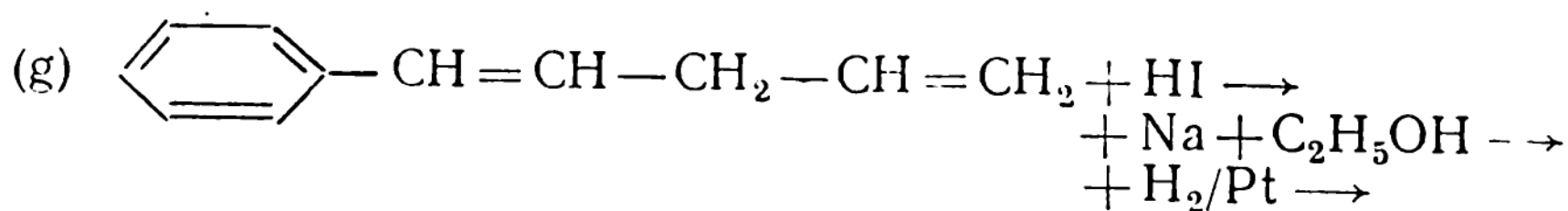
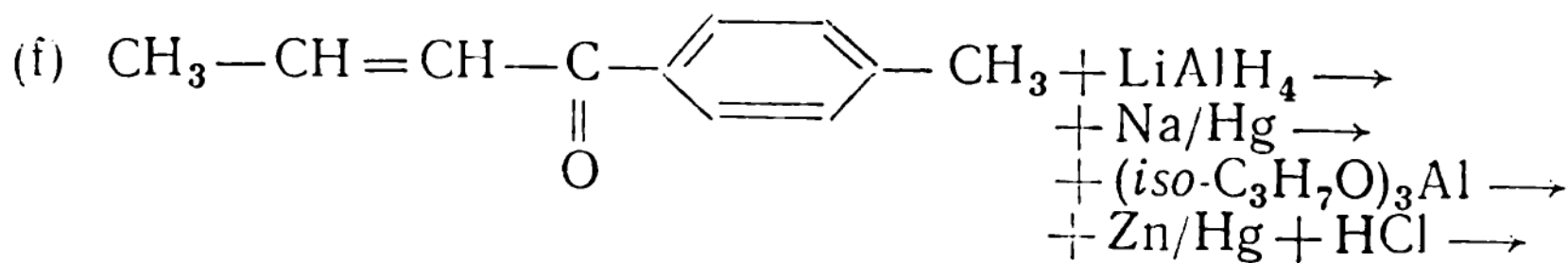
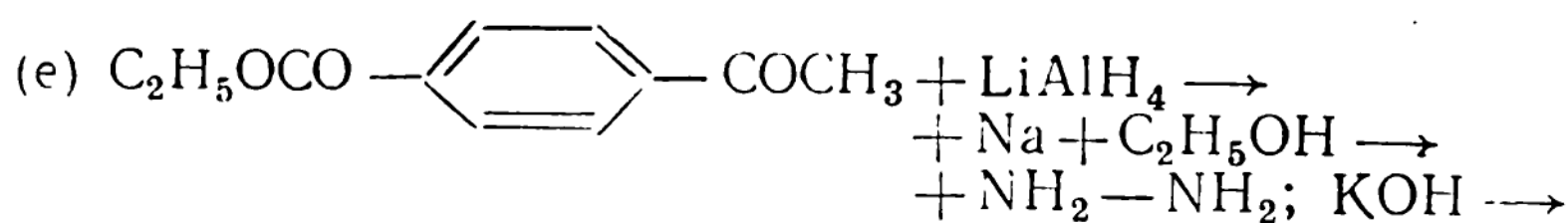
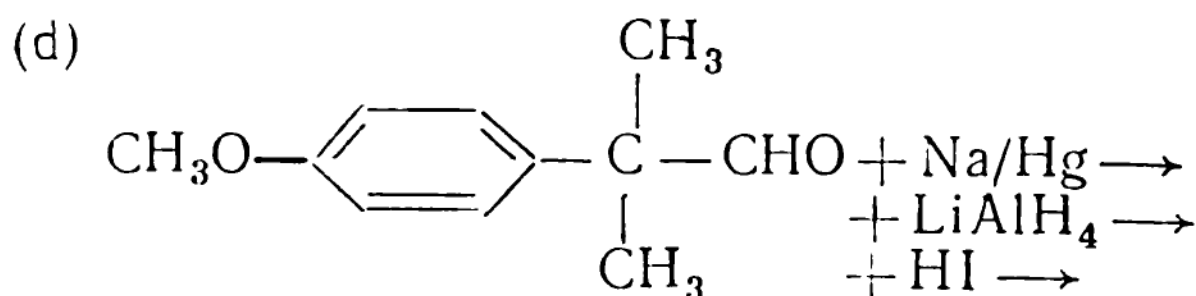
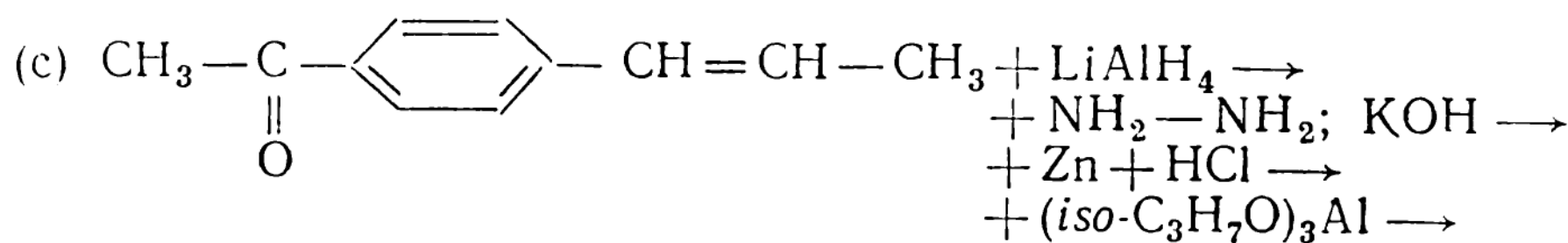
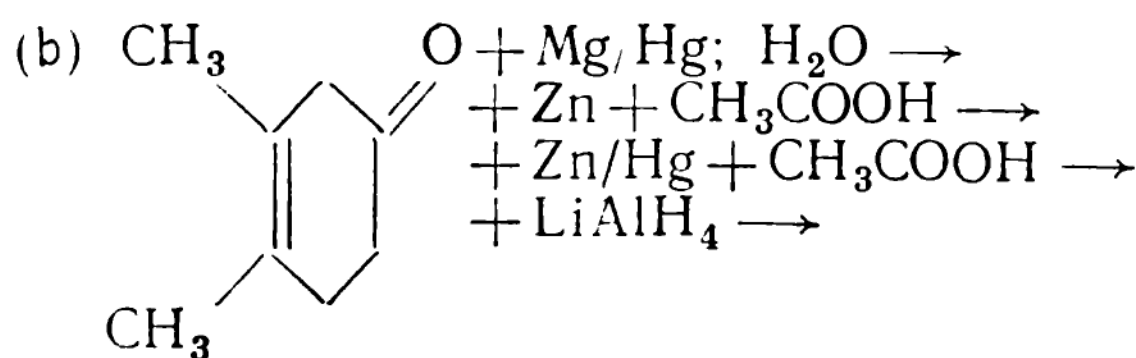
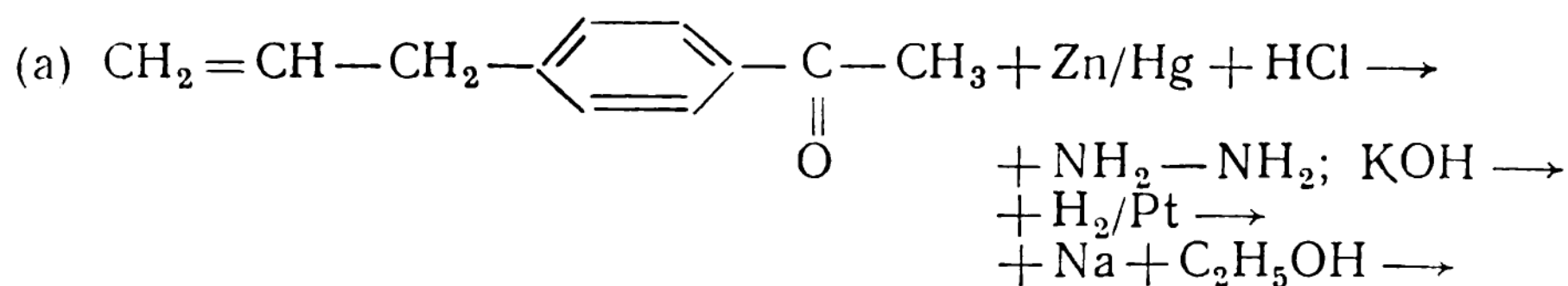
8. What theories of catalytic hydrogenation do you know? What are the facts on which these theories are based?

9*. What experiments would you suggest for elucidation of the mechanism of the Cannizzaro reaction? For one thing, can it be found what compound transfers hydrogen to the aldehyde group when the latter is converted into the alcoholic group?

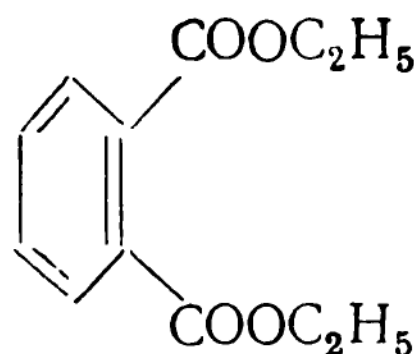
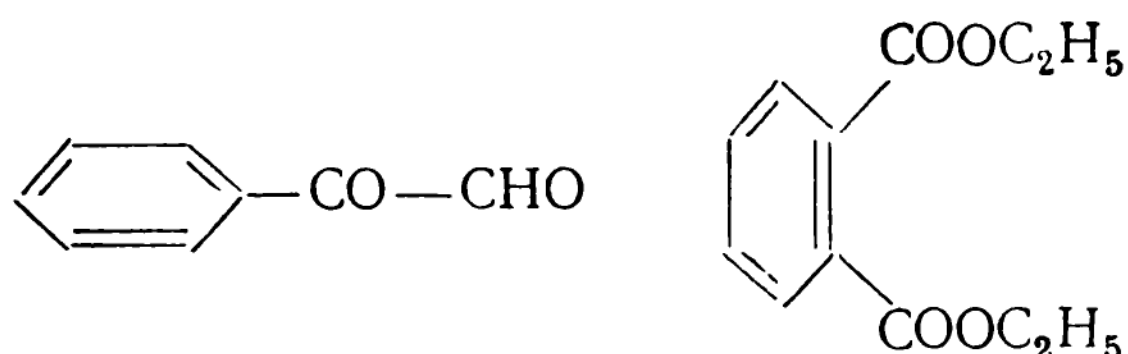
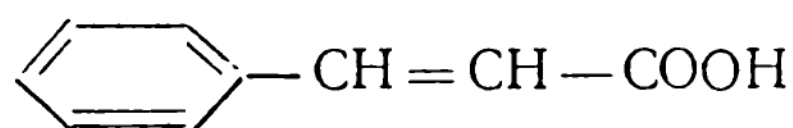
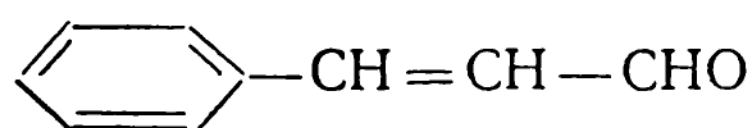
10*. How would you explain the fact, taking into account the reaction mechanism, that carbonyl compounds when subjected to the action of active metals (Na, Mg, Al, Zn)

are reduced to dimeric reaction products in an aprotic medium and to monomeric ones in protic solvents?

11. Complete the following equations:

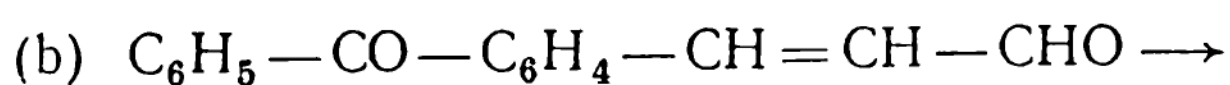
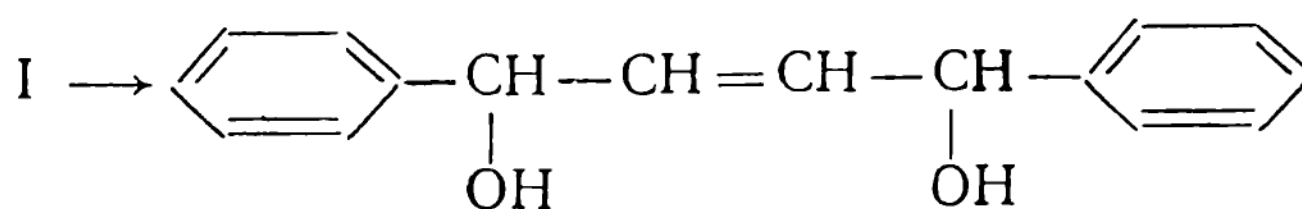
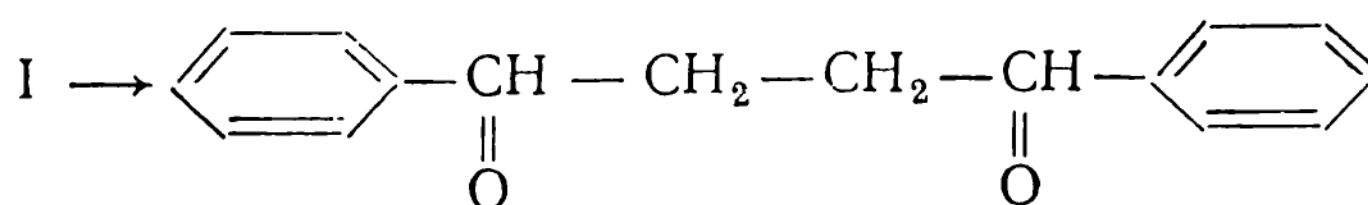
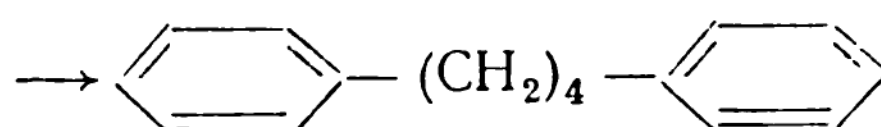
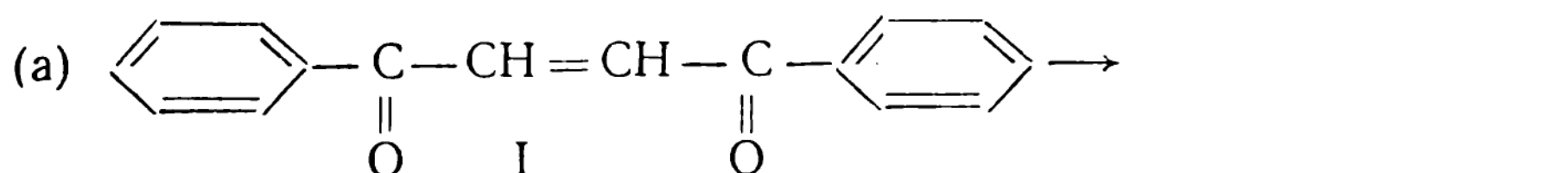


12*. Could you vary the sequence of reduction of multiple bonds and functional groups in the following compounds?

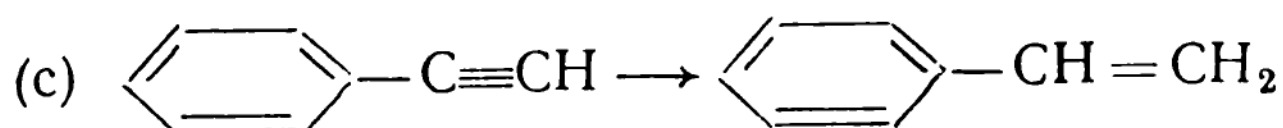
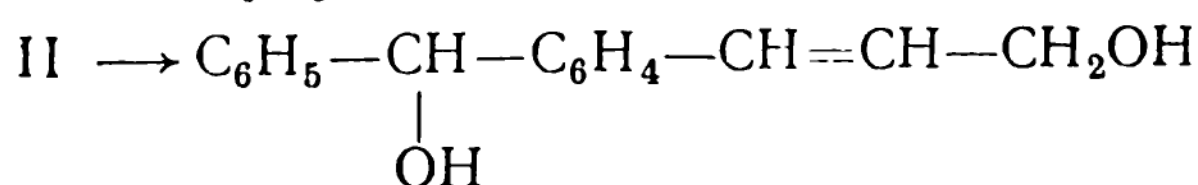
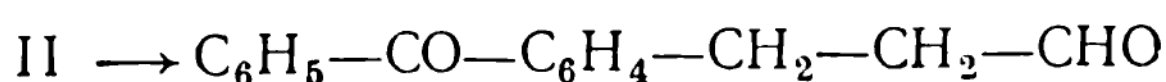


What methods must be used for this purpose?

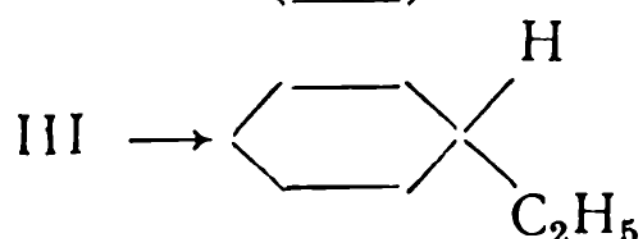
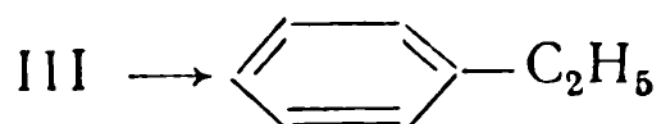
13*. How can the following conversions be accomplished?

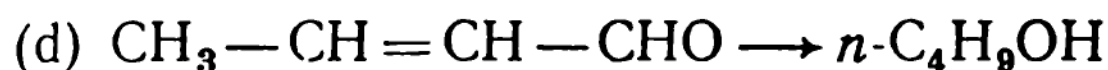


II



III

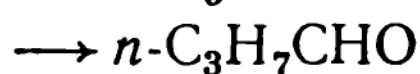
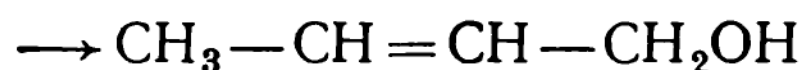




IV

IV

IV



14*. Indicate at least three routes for the conversion $>\text{C}=\text{O} \longrightarrow >\text{CH}_2$.

15*. Show how the conversion of a carboxylic acid into an aldehyde can be accomplished by using different methods.

16*. Consider the effect exerted by amalgamation on the reduction of carbonyl compounds by metals (Mg, Al, Zn).

17*. Consider in detail the steps of the synthesis of pentaerythritol.

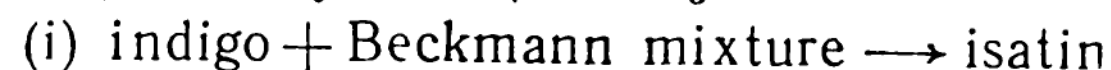
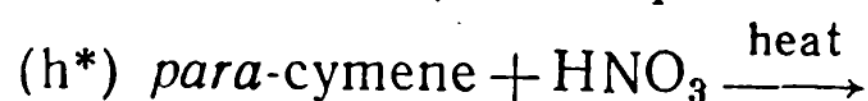
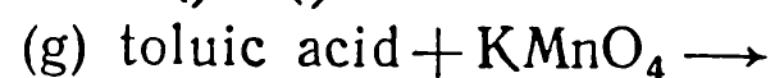
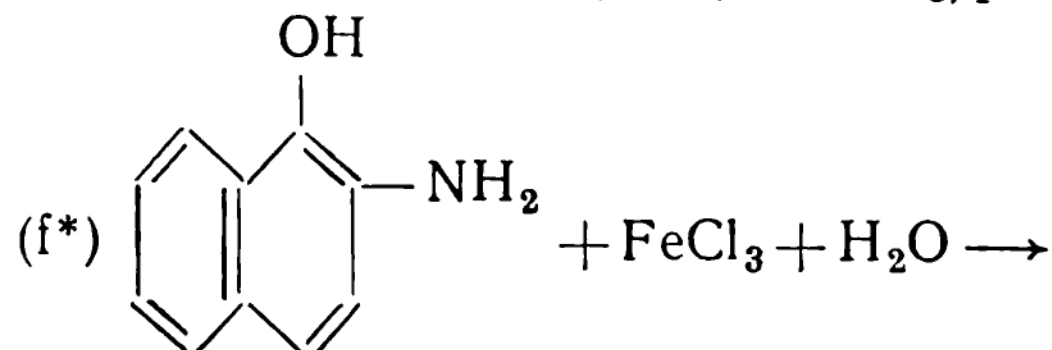
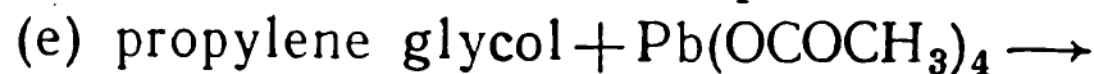
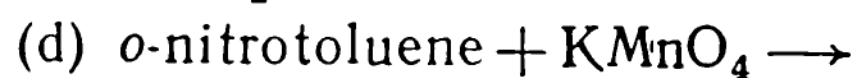
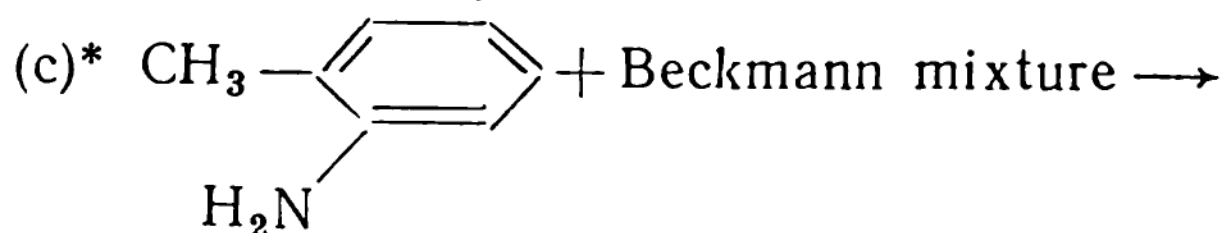
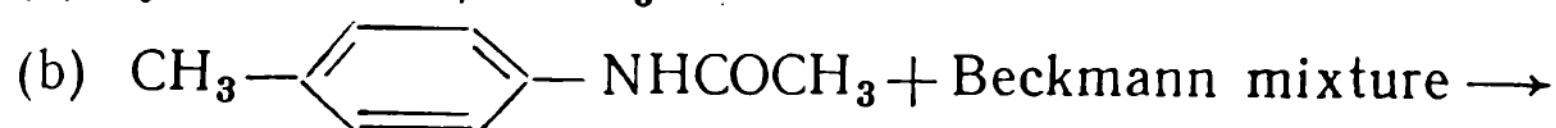
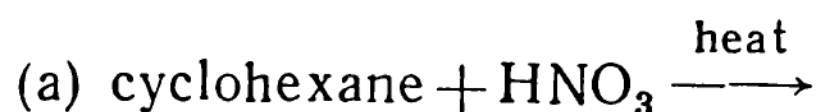
18*. Derive 3,4-diethylhexa-2,4-diene and pinacol, $(\text{C}_2\text{H}_5)_2\text{C}(\text{OH})-\text{C}(\text{OH})(\text{C}_2\text{H}_5)_2$, from propionic acid.

19*. What substances are obtained by the action of aluminium amalgam on acetophenone? What type of isomerism is observed in these compounds?

20. What methods are used in practice to prepare catalysts in a finely divided state?

3. OXIDATION

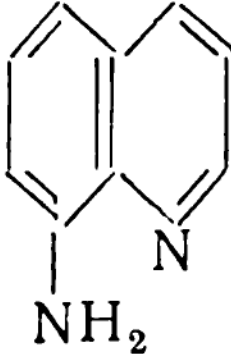
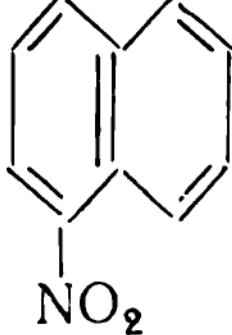
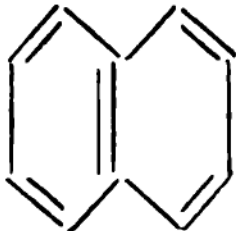
21. Complete and balance the following reaction equations:



22. Complete and balance the following equations:

- (a) toluene + $\text{Pb}(\text{OCOCH}_3)_4 \rightarrow$
 $+ \text{CrO}_3 + \text{CH}_3\text{COOH} \rightarrow$
 $+ \text{SeO}_2 + \text{CH}_3\text{COOH} \rightarrow$
 $+ \text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4 \rightarrow$
 $+ \text{CrO}_2\text{Cl}_2 \rightarrow$
- (b) di-*p*-tolyl ketone + $\text{Pb}(\text{OCOCH}_3)_4 \rightarrow$
 $+ \text{CrO}_2\text{Cl}_2 \rightarrow$
 $+ \text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4 \rightarrow$
- (c) allylbenzene + KMnO_4 (dil. sol., in the cold) $\rightarrow$
 $+ \text{KMnO}_4$ (conc. sol., boiling) $\rightarrow$
 $+ \text{Pb}(\text{OCOCH}_3)_4 \rightarrow$
 $+ \text{SeO}_2 \rightarrow$
 $+ \text{O}_3$ (1 mole); $\text{H}_2\text{O} \rightarrow$
 $+ \text{C}_6\text{H}_5\text{COOOH} \rightarrow$
 $+ \text{Beckmann mixture} \rightarrow$
- (d) *o*-toluidine + $\text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4 \rightarrow$
 $+ (\text{CH}_3\text{CO})_2\text{O}; \text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4 \rightarrow$
- (e) methyl-*p*-tolyl ketone + $\text{Cl}_2 + \text{NaOH} \rightarrow$
 $+ \text{KMnO}_4 \xrightarrow{\text{heat}}$
 $+ \text{CrO}_3 + (\text{CH}_3\text{CO})_2\text{O} \rightarrow$
 $+ \text{SeO}_2 \rightarrow$

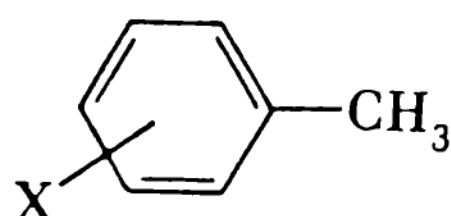
23*. Consider the scheme of successive oxidation of the following compounds:

- (a) $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$ (b)  (c) 
- (d) 
- (e) $\text{CH}_3-\text{C}_6\text{H}_4-\text{CH}_2-\text{CHO}$
- (f) $\text{CH}_3-\text{CH}=\text{CH}-\text{C}_6\text{H}_4-\text{CH}_3$
- (g) $\text{CH}_2=\text{CH}-\text{CHO}$

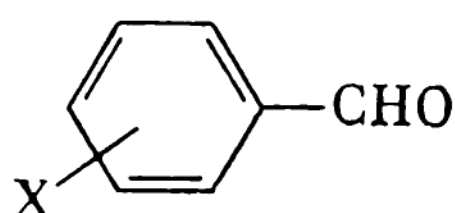
Could you change the sequence of oxidation in the examples given above? If so, what methods must be employed?

24*. Name several methods for conversion of a primary alcohol into an aldehyde having the same number of carbon atoms. Explain why the oxidation of a primary alcohol by the Beckmann mixture is applicable for preparing aldehydes C_2 - C_5 and can hardly be used for producing, say, aldehyde C_{10} .

25*. Indicate the routes for conversion of substituted toluenes



(where $X = \text{Hal}, \text{NO}_2$) into substituted benzaldehydes

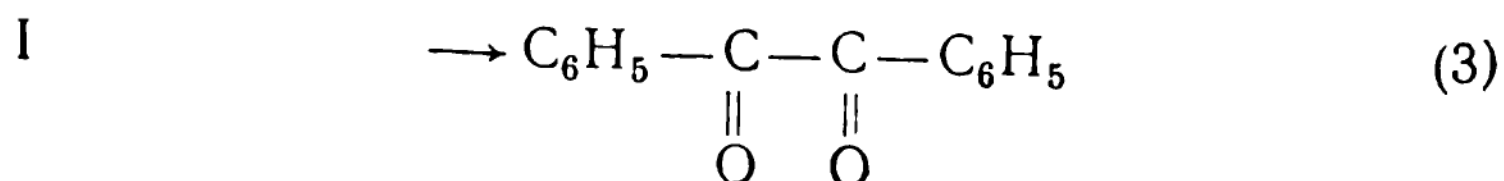
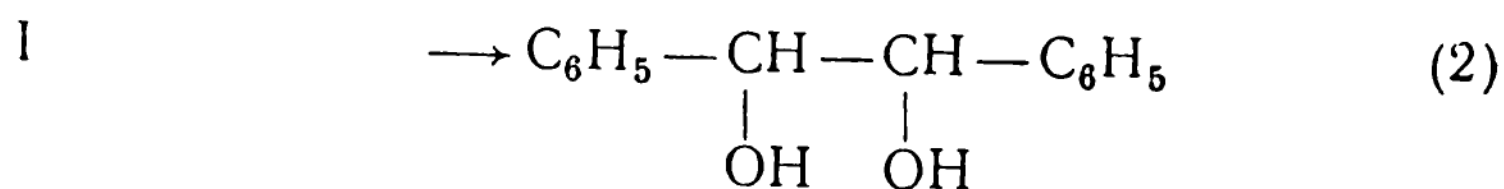
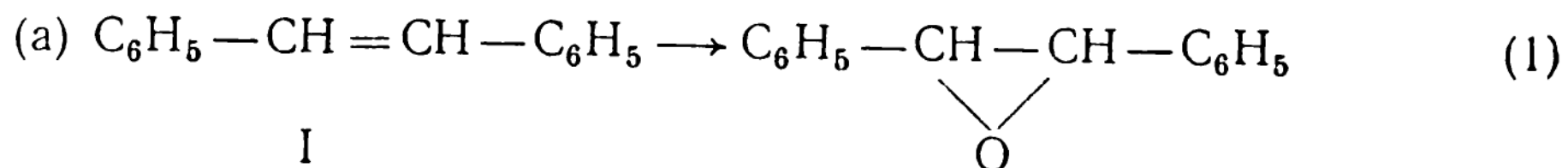


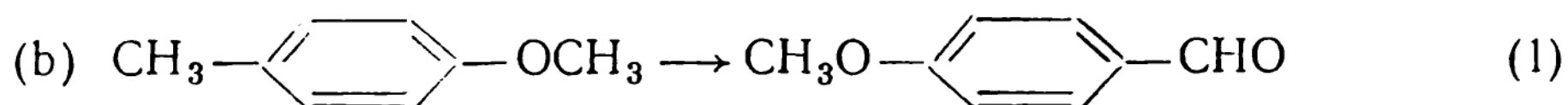
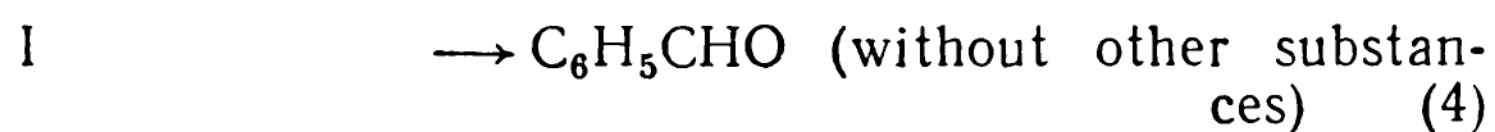
26*. In the oxidation of secondary alcohols according to Oppenauer use is usually made of acetone and aluminium *tert*-butylate. Consider the mechanism of this reaction and explain why *tert*-butylate is used, and not other aluminium alkoxides.

27*. Why are ketones easily oxidized in an acidic solution (Beckmann mixture, nitric acid)? Explain why the oxidation of ketones may lead to the formation of several acids. In what cases does the oxidation of ketones result in only one acid and in what cases in only two?

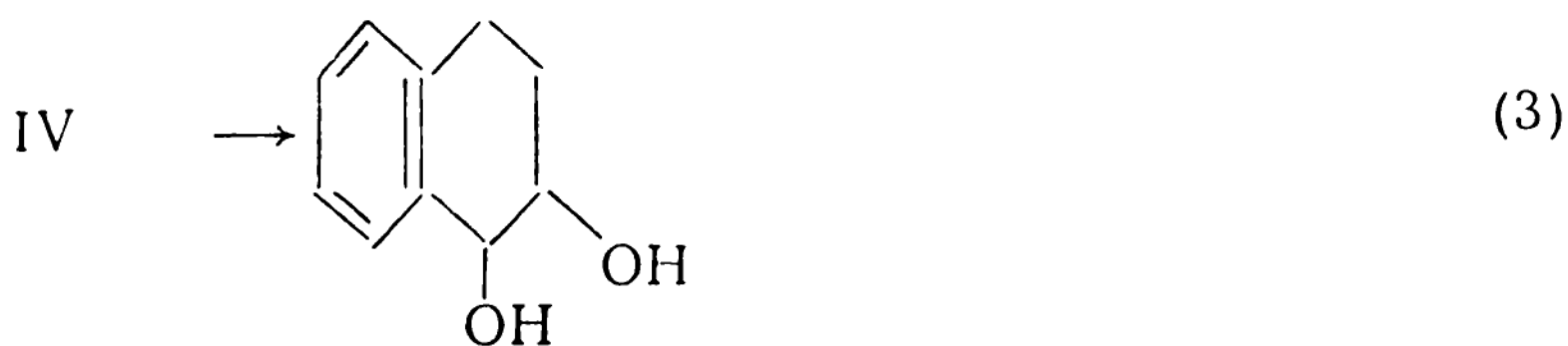
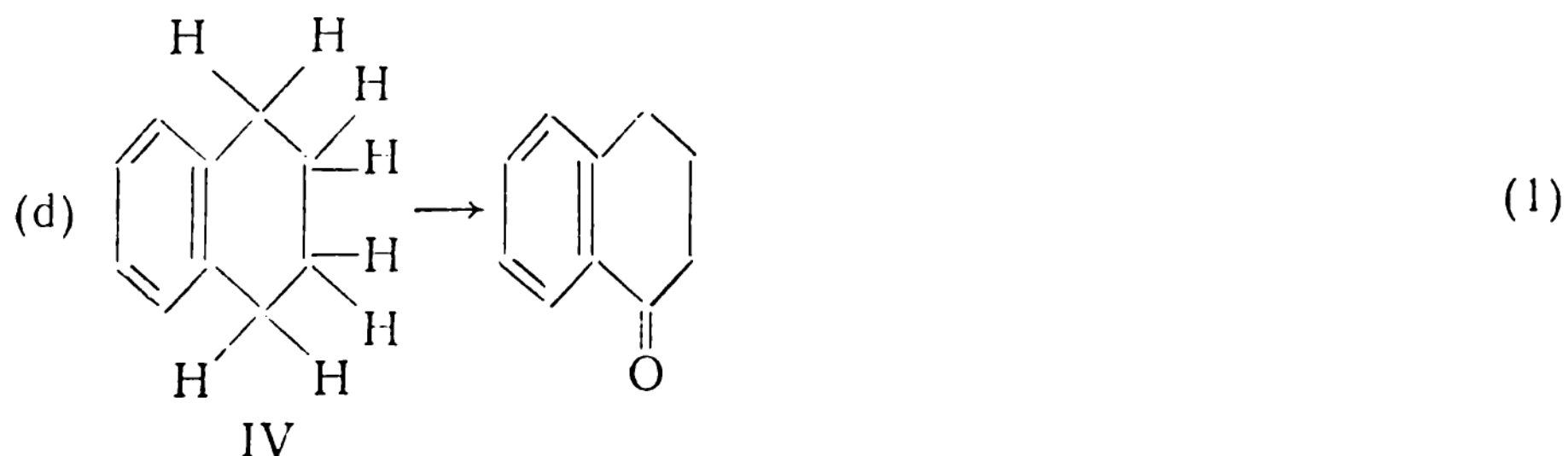
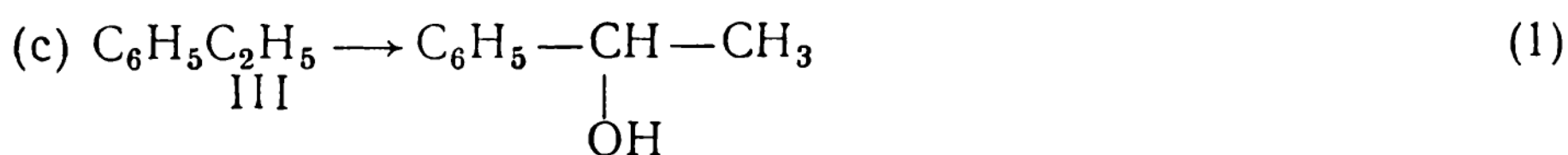
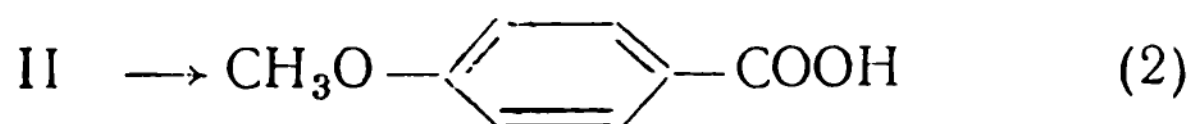
28. How does the oxidation of 2-methylcyclopentanone proceed under severe conditions?

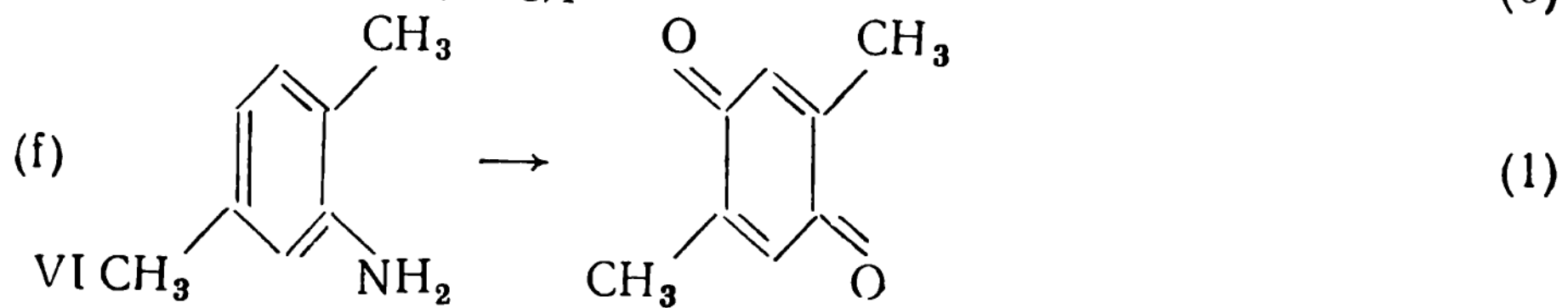
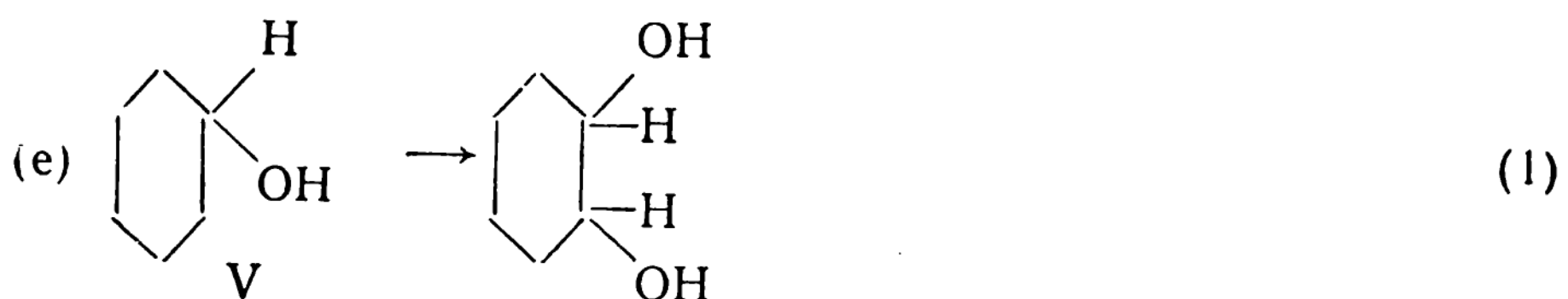
29* How can the following conversions be accomplished:

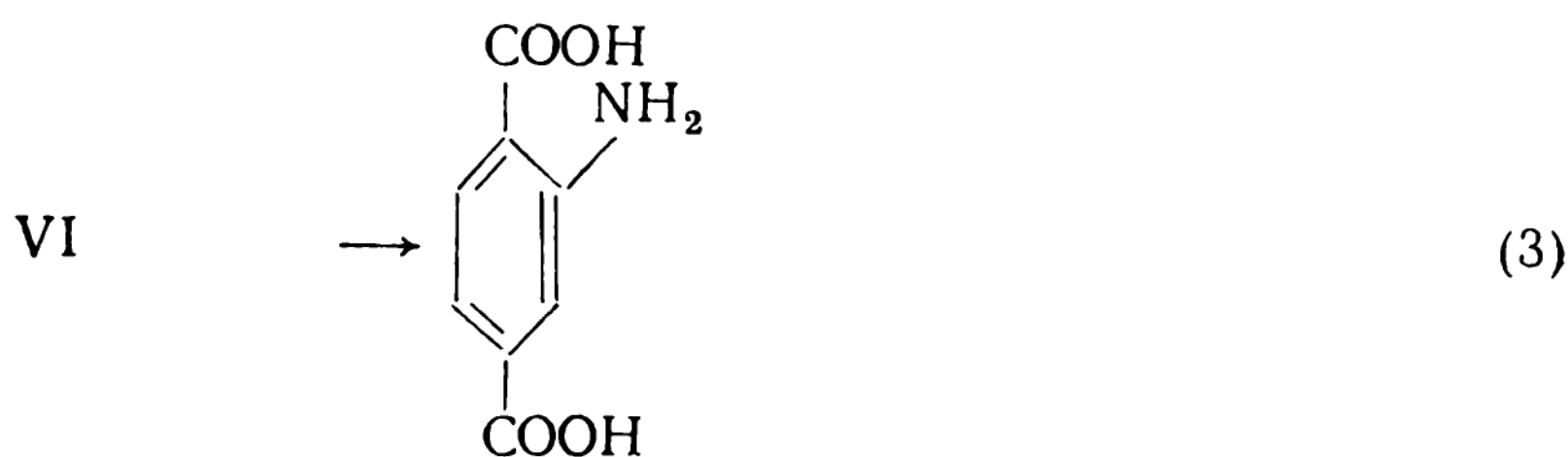
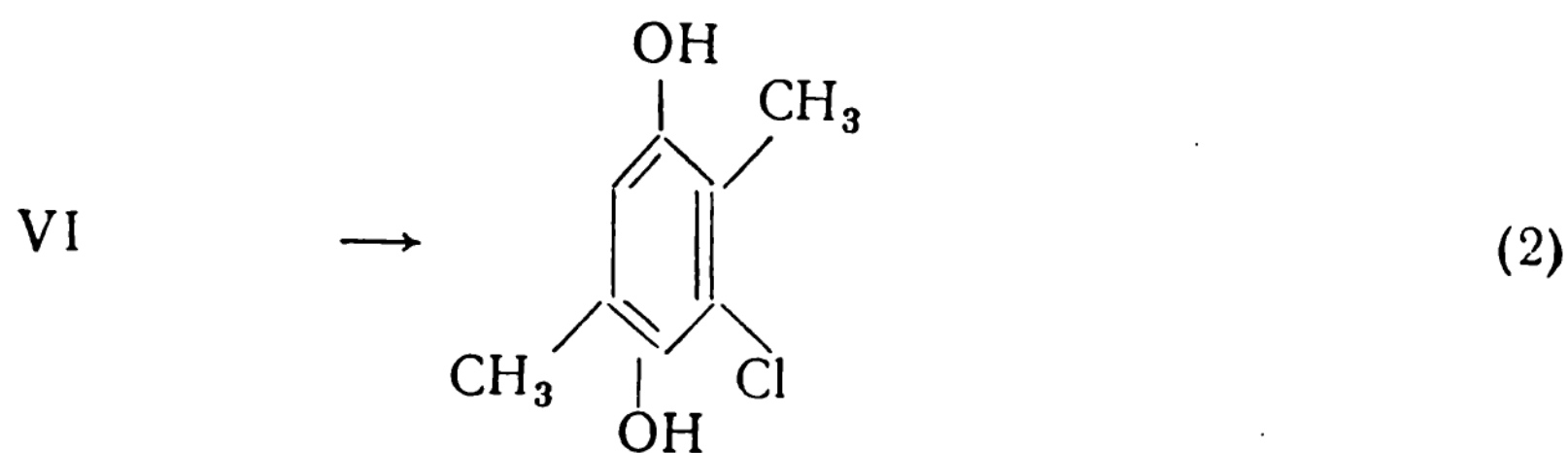




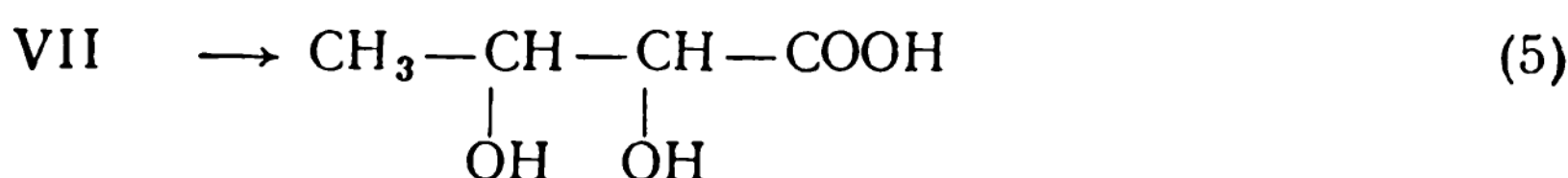
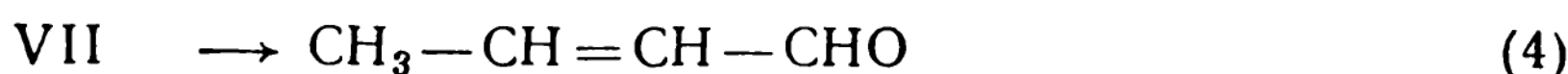
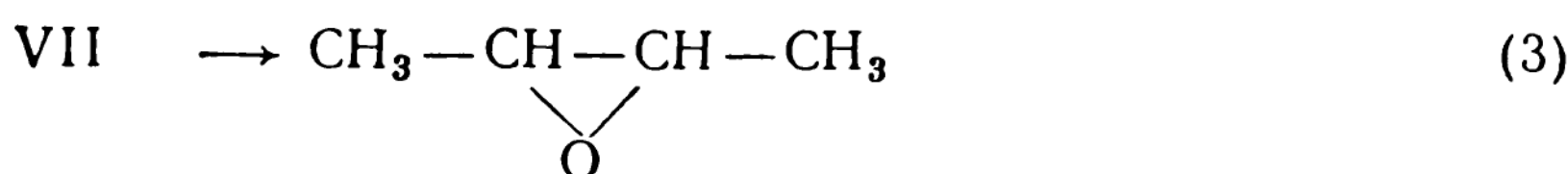
II







VII



30*. Prepare from ethanol 1-ethoxy-1-hydroxy-2,2,2-trichloroethane.

31*. Using *p*-acetyethylbenzene as the starting material, prepare (a) *p*-diacetylbenzene, and (b) *p*-ethylbenzoic acid.

32. Prepare anesthine and novocaine from *p*-toluidine.

33*. Show how *p*-tolualdehyde can be converted into *p*-carboxybenzaldehyde.

34*. How can geraniol be converted to citral?

35*. Using ethyl maleate as the starting material, prepare ethyl glyoxylate.

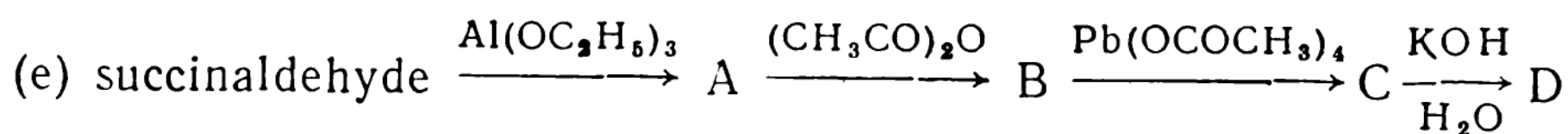
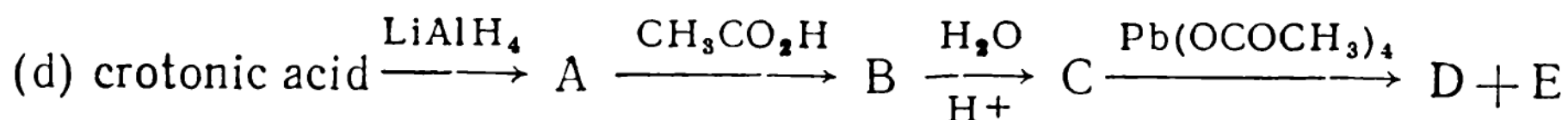
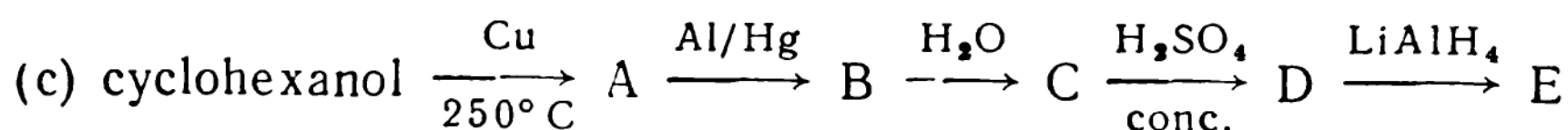
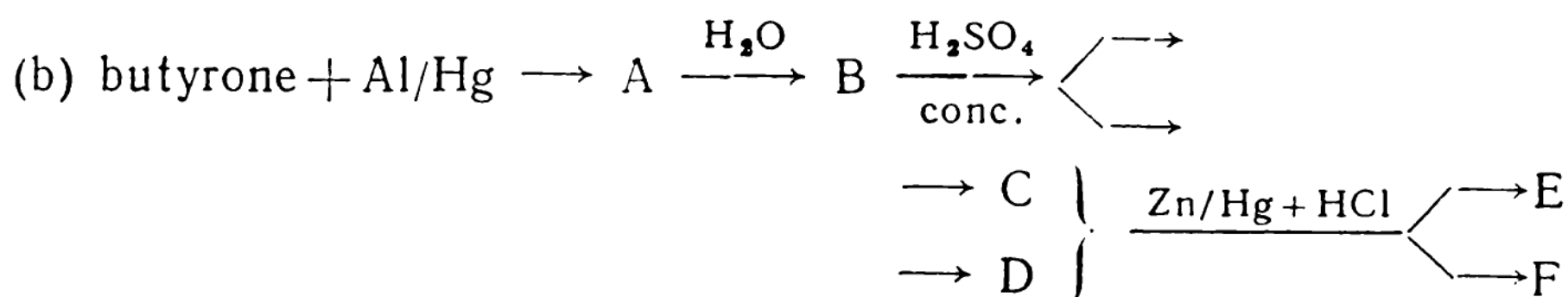
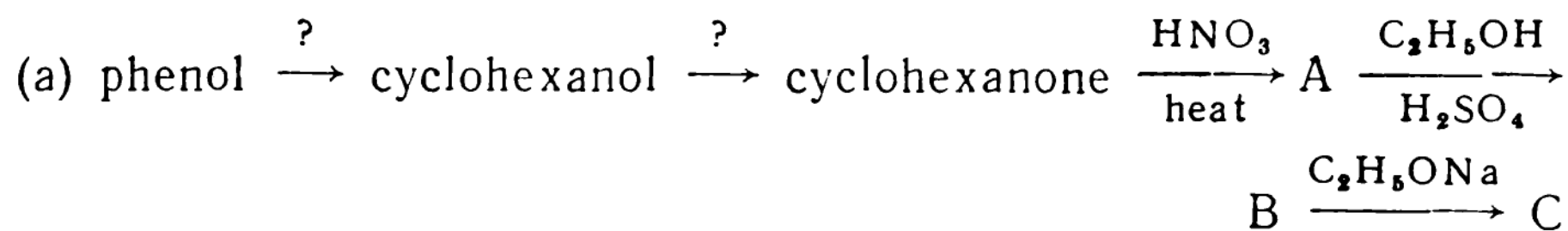
36*. Derive γ -acetylvaleric acid from 1-methylcyclohex-1-ene.

37*. Prepare γ -acetylbutyric acid from methyl iodide and cyclopentanone (without using other organic reagents).

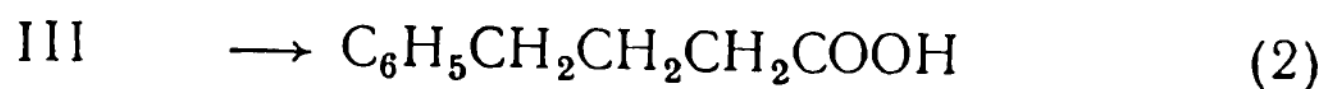
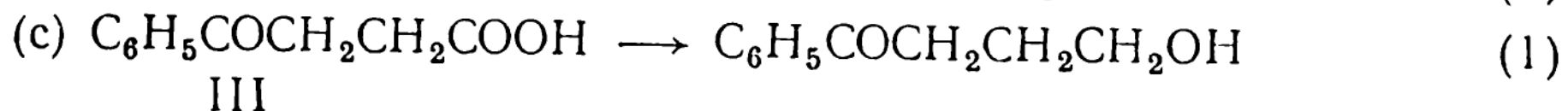
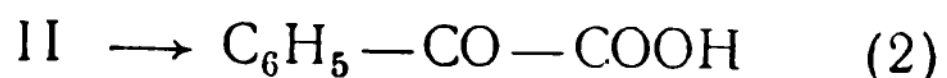
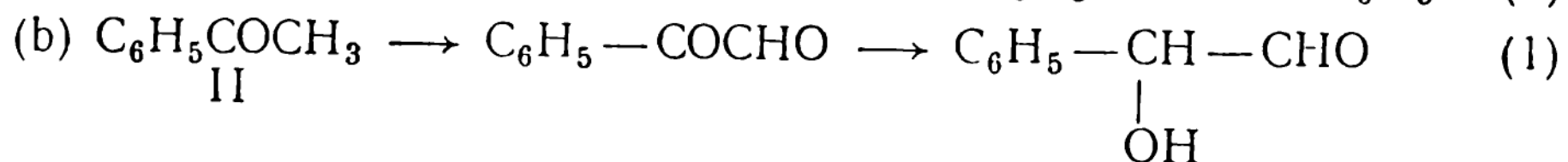
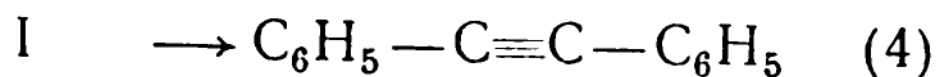
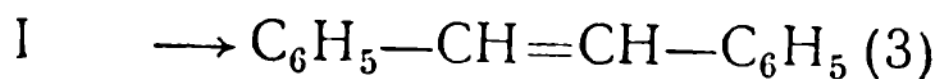
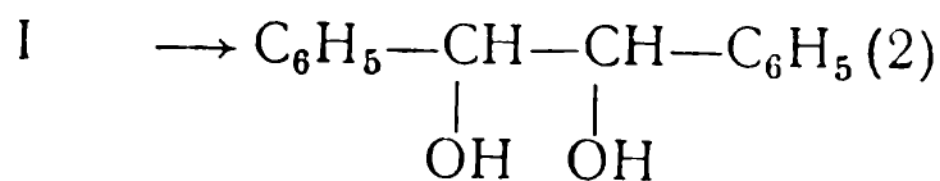
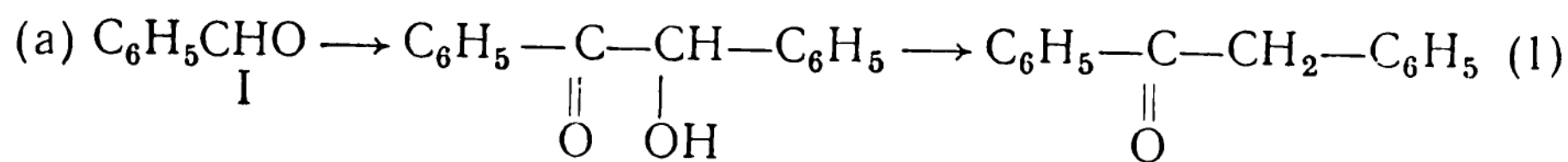
38. Derive δ -benzoylvaleric acid from bromobenzene and cyclohexanone (without using other organic reagents).

4. COMBINATION PROBLEMS

39*. Write the reactions:



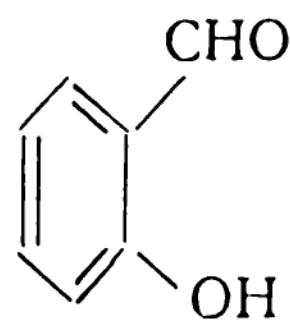
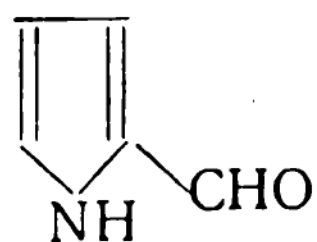
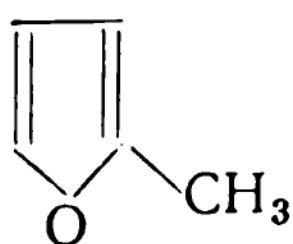
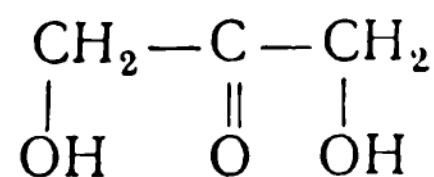
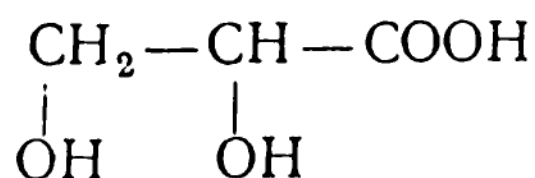
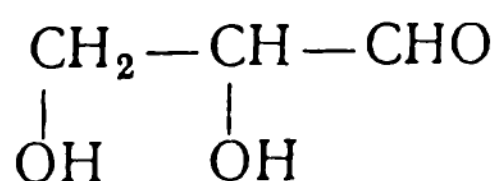
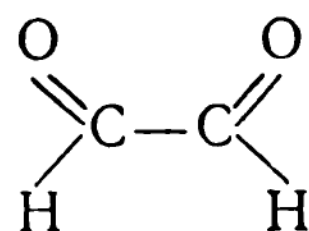
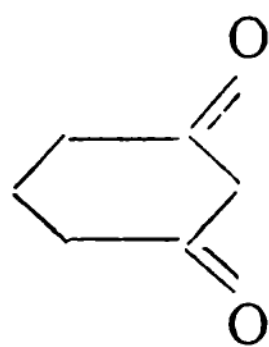
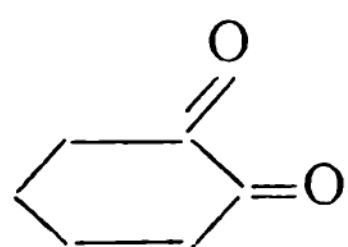
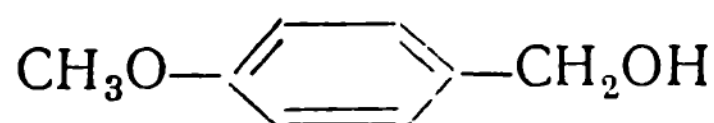
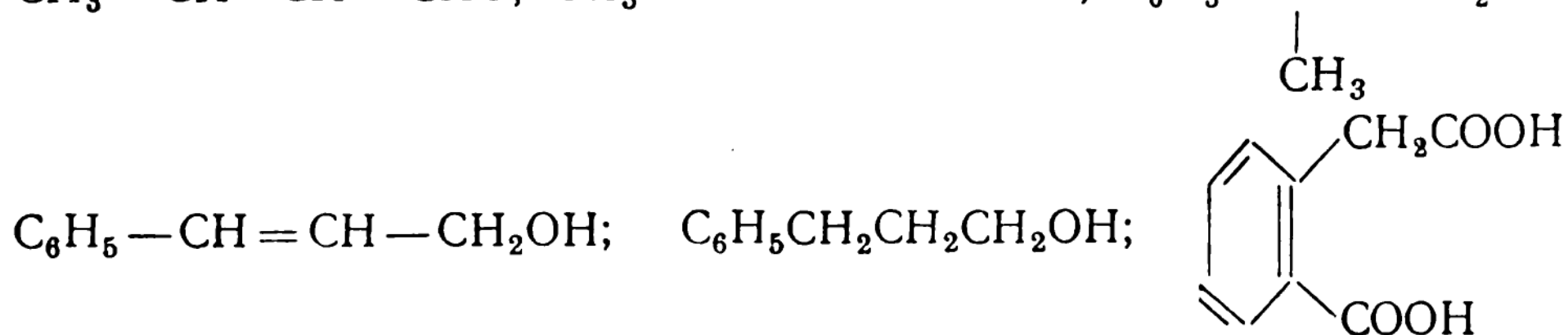
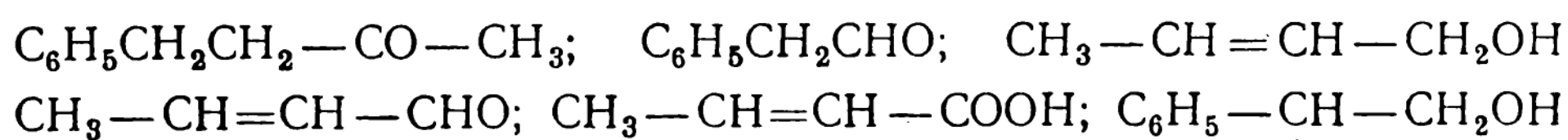
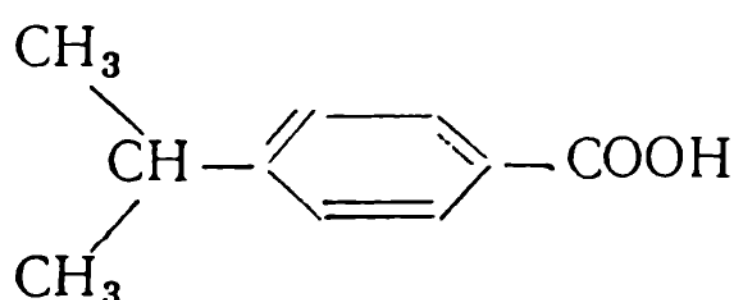
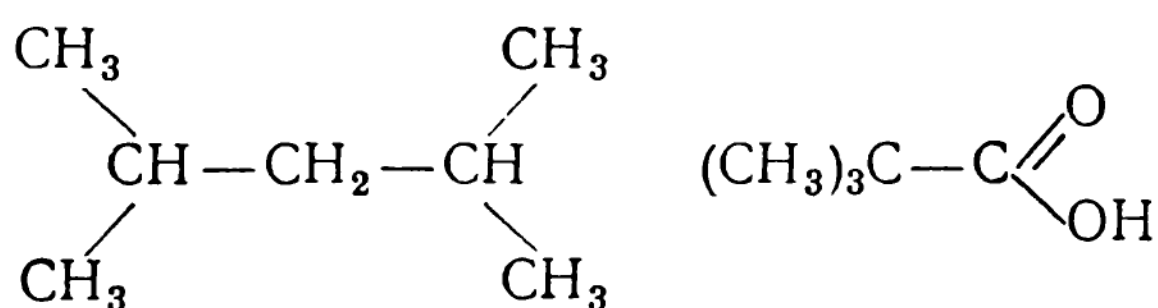
40*. How can the following conversions be accomplished?

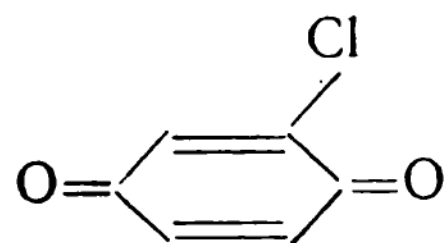
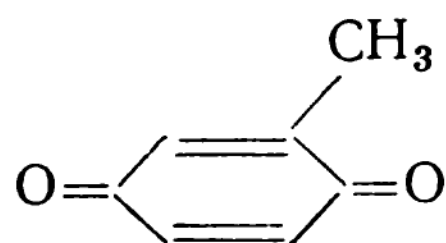
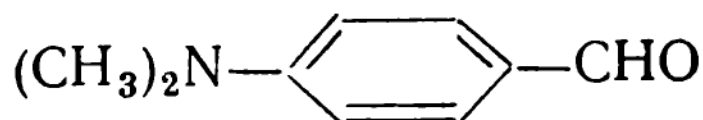
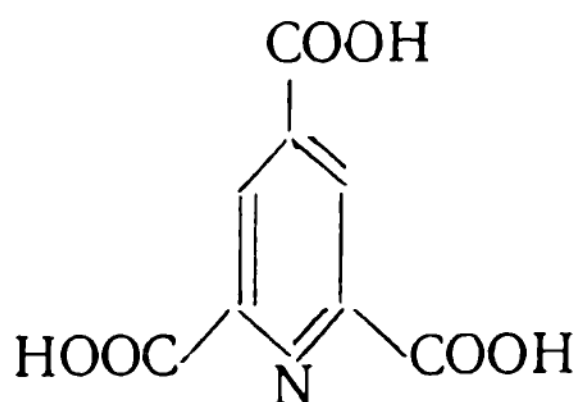
41*. Prepare γ -ketobutylbenzene from toluene and ethanol.

42*. How can cyclopentanone be made from phenol?

43*. Prepare *cis*- and *trans*-cyclohexane-1,2-diols from phenol.

44. What methods would you suggest for synthesis of the following compounds?

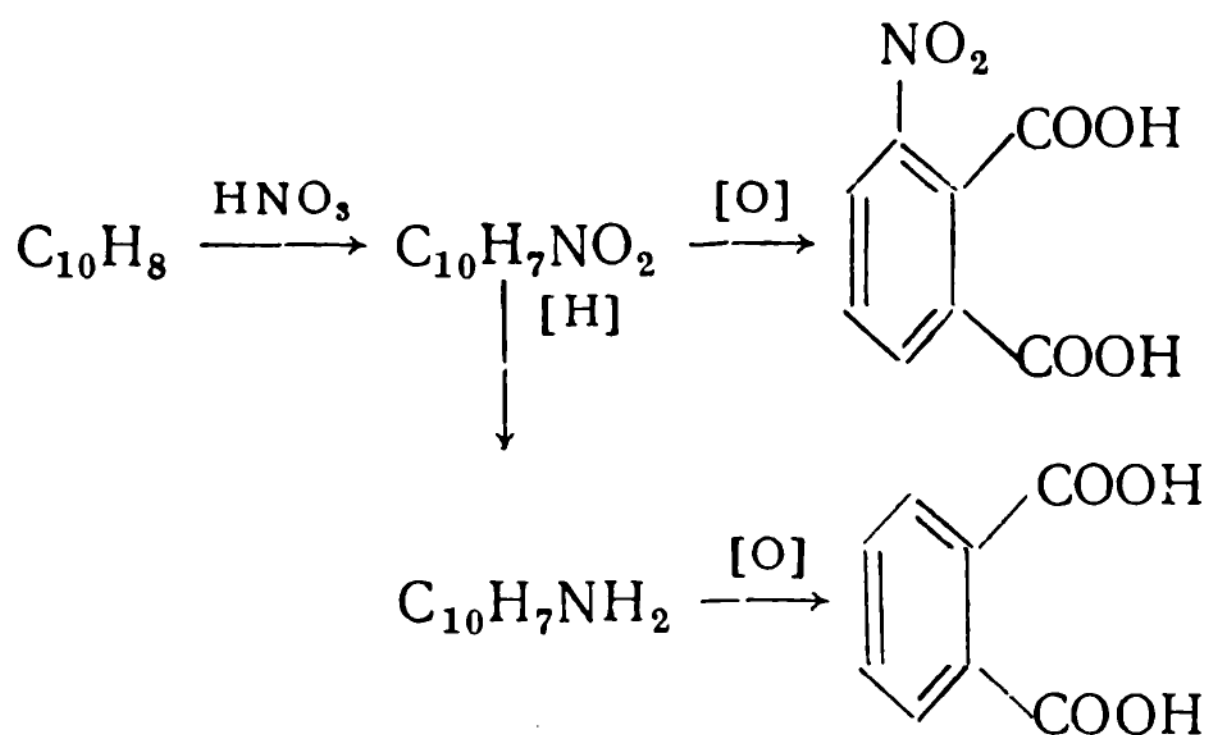




Compare these methods as to the availability of starting materials and the convenience in carrying out the syntheses.

5. STRUCTURE DETERMINATION

45. What was the significance of the following series of conversions in proving the structure of an initial starting hydrocarbon in the history of organic chemistry?



46*. What reactions can be used to distinguish between butane-1,3-diol and butane-2,3-diol?

47*. Two hydrocarbons, each having the general formula C_4H_8 , absorb readily one mole of hydrogen when subjected to hydrogenation over platinum; are converted to the compounds C_4H_8O by the action of perbenzoic acid; and on ozonolysis form only acetaldehyde. Suggest structures for these compounds.

48*. The ozonolysis of one of xylene isomers led to the formation of glyoxal, methyl glyoxal, and dimethyl glyoxal. What is the structure of this xylene?

49*. The oxidation of the hydrocarbon C_9H_{10} by an alkaline solution of permanganate led to terephthalic acid. What is the structure of the starting hydrocarbon? Could you answer this question unambiguously if the hydrocarbon had the structure $C_{10}H_{12}$?

50*. When a hydrocarbon was subjected to ozonolysis, a mixture of acetylacetone and propionaldehyde resulted. What could be the structure of the original hydrocarbon? What additional information must one have in order to give an unambiguous answer?

51*. The oxidation of a hydrocarbon resulted in the formation of only 2-methyladipic acid. What is the structure of the starting material? What else do you need to know in order to give an unambiguous answer?

52*. The alcohol $C_6H_{14}O$ can be converted by dehydration into the olefin C_6H_{12} , which when oxidized by the dichromate oxidizing mixture forms only acetone. What is the structure of the alcohol? Is your answer unambiguous?

53*. One mole of a hydrocarbon absorbed 1 mole of hydrogen in the presence of a platinum catalyst. The ozonolysis of the resulting compound gave a mixture of acetone and acetaldehyde. What might be the structure of the starting hydrocarbon?

54*. The compound C_5H_8O adds bromine to give $C_5H_8Br_2O$, does not react with an ammonia solution of silver oxide but enters into the reaction with phenylhydrazine. Determine the structure of this compound given that its ozonolysis yields acetaldehyde and the substance $C_3H_4O_2$, which loses readily carbon monoxide to form acetaldehyde.

55*. Formulate the structure of the compound $C_7H_{12}O$ if it is known that the oxidation of this compound by selenium dioxide results in a mixture of two substances, $C_7H_{10}O_2$, and when subjected to the action of hot concentrated nitric acid it forms a mixture of 2- and 3-methyladipic acids.

What products are formed if the compound $C_7H_{12}O$ is subjected to the action of magnesium amalgam and of zinc amalgam in an acidic medium?

56*. The ozonolysis of the hydrocarbon C_9H_{16} led to the formation of formaldehyde, acetaldehyde and a diketone, $C_6H_{10}O_2$, in a molar ratio of 1 : 1 : 1. To ascertain the structure of the diketone, it was brought into reaction with

excess methylmagnesium iodide; the product of this reaction when heated with potassium bisulphite gave largely 2,5-dimethylhexa-2,4-diene. Formulate the structure of the initial hydrocarbon.

57*. Write the structure of the substance $C_6H_{12}O_4$, one mole of which when subjected to the action of metallic sodium yields two moles of hydrogen; the action of periodic acid (or lead tetraacetate) on it leads to only one product— $C_3H_4O_2$. The last-named compound reacts with dinitrophenylhydrazine and on oxidation gives the compound $C_3H_4O_4$, which on heating readily loses carbon dioxide.

58*. The ozonolysis of the substance $C_{10}H_{16}O_4$ leads to the sole product of oxidation, $C_5H_8O_3$. The hydrolysis of the latter yields an acid and an alcohol. On heating the acid gives off carbon monoxide and the alcohol gives a positive haloform reaction.

If the compound $C_{10}H_{16}O_4$ is subjected to hydrolysis, acid A will result, which on prolonged heating gives $C_6H_6O_3$. This compound can react with water to form acid B which is of the same composition as A but has a different melting point. What is the structure of the compound $C_{10}H_{16}O_4$?

How many substances will be formed by the action of a dilute solution of potassium permanganate on a mixture of the acids A and B in the cold?

59*. When the substance $C_6H_{12}O_6$ is subjected to the action of methanol in the presence of hydrogen chloride, it is converted to $C_7H_{14}O_6$, which is converted into $C_{11}H_{22}O_6$ by the action of dimethyl sulphate in an alkaline medium. The acid hydrolysis of $C_{11}H_{22}O_6$ leads to $C_{10}H_{20}O_6$, which on oxidation by nitric acid forms carbon dioxide and $C_8H_{14}O_7$. The last-named oxidation-resistant compound turns litmus red and can react with two alkali equivalents. What could you say about the structure of the starting substance, $C_6H_{12}O_6$?

60*. A compound of the composition $C_5H_{12}O$ forms $C_5H_{10}O$ on dehydrogenation (the substance formed colours a solution of fuchsinsulphurous acid) and when heated with concentrated sulphuric acid it gives the hydrocarbon C_5H_{10} .

The passage of dry hydrogen bromide into $C_5H_{12}O$ results in the formation of two bromides. The one that is formed in a large quantity reacts readily with dilute alkalis and the

other remains practically unchanged on boiling even with concentrated alkalis but reacts readily with moist silver oxide. In both cases one of the reaction products is the substance $C_5H_{12}O$, which is different from the original one. The hydrolysis is accompanied by the formation of a hydrocarbon, C_5H_{10} , the compound that is formed from the original substance by the action of sulphuric acid. When strongly oxidized by a Beckmann mixture this hydrocarbon forms only acetic acid and carbon dioxide.

Write equations for these reactions and discuss their mechanism.

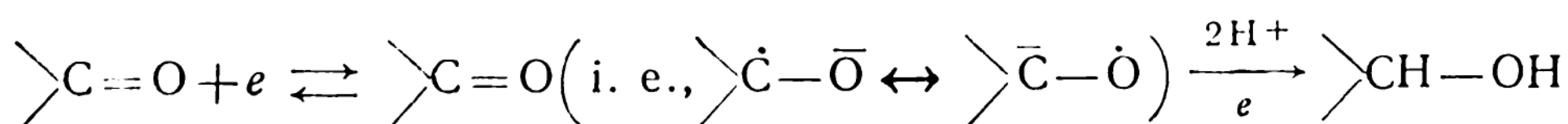
Answers

1. Any electrophile is an electron acceptor and is therefore, in a general sense, an oxidant just as any nucleophile is a reducing agent.

5. The reducing agent is the carbon of the carboxyl group which is converted into a carbonate.

9. The hydrogen atoms of water should be tagged (simultaneously, as a result of the exchange, the hydrogen atoms of the hydroxyl groups of the base used as a catalyst will also be tagged) and in the other experiment, the hydrogen atoms of the aldehyde groups, and the distribution of the tagged species (deuterium, preferably) should be traced in the reaction products. To ascertain the effect of the nature of the catalyst one should examine the kinetics of the reaction caused by bases of different strength and cations differing in their complex-forming ability. For more detail see J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

10. If a sufficiently stable anion-radical is formed when an electron is transferred to the carbonyl group, it could be dimerized (for example, the synthesis of pinacols from ketones, of acyloins from esters or acid chlorides, the dihydrobenzoin condensation of aromatic aldehydes). In a protic medium the anion-radical adds readily a proton and is converted into a radical, which is then quickly reduced:



In consequence of this, carbonyl compounds capable of enolization can give, on reducing dimerization even in an aprotic medium, certain amounts of monomeric reduction products and condensation products (at the expense of the enolate formed).

12. To reduce the aromatic nucleus with the functional groups being unchanged is impossible. Cinnamaldehyde can be converted into cinnamic alcohol by the Meerwein-Ponndorf-Verley mechanism or by adding, at a low temperature, an exact equivalent of lithium aluminium hydride (the reverse order of addition or an excess of lithium aluminium hydride leads to hydrocinnamic alcohol). Cinnamaldehyde can be produced by catalytic hydrogenation using acetal protection. Cinnamic acid can be easily converted into hydrocinnamic acid by the action of sodium amalgam or by catalytic hydrogenation. Phenylglyoxal forms selectively acetal and therefore the keto group can be reduced selectively. The selective reduction of an aldehyde group is more difficult to accomplish (the Cannizzaro reaction leads to mandelic acid).

13. (a) According to Clemmensen; for example, with amalgamated sodium or H_2/Pt (1 mole); the Meerwein-Ponndorf-Verley reduction.

(b) Na/Hg ; the Meerwein-Ponndorf-Verley reduction.

(c) H_2/Pt or Na/NH_3 (liquid); H_2/Pt ; H_2/Pt .

(d) H_2/Pt ; the Meerwein-Ponndorf-Verley reduction or LiAlH_4 ; acetal protection, hydrogenation, hydrolysis.

14. The Kishner reaction; the Clemmensen reaction; reduction to an alcohol, dehydration, hydrogenation.

15. Reduction of the acid by formic acid over MnO_2 or ThO_2 ; the Rosenmund reduction; reduction of a nitrile according to Stephen; reduction of the acid nitrile or amide by lithium aluminium hydride.

16. The metal-acid system reduces the carbonyl group to an alcoholic, as a general rule; amalgamated metals reduce ketones in an aprotic medium to pinacols; amalgamated zinc reduces the carbonyl group in an acidic medium to a methylene group (the Clemmensen reaction).

17. Successive aldol condensation reactions followed by the Cannizzaro reaction.

18. Use must be made of the catalytic conversion of the

acids to symmetric ketones, reduction to pinacols and dehydration. The diene is formed in competition with pinacolin.

19. A mixture of stereoisomeric pinacols, a small amount of α -phenylethyl alcohol and products of acetophenone condensation.

21. (c) Toluquinone. (f) 1,2-Naphthoquinone. (h) *p*-Toluic acid.

23. In cases *a-d* the aromatic nucleus is reduced to a quinoid one and the quinone is further oxidized. The deep oxidation of substance (a) leads to acetic acid and that of (b) and (f) to the corresponding dibasic acids. The nucleus of *p*-toluidine can be protected against oxidation by acetylation of the amino group, as a result of which there appears the possibility of selective oxidation of the methyl group to a carboxyl one. The aldehyde groups of (e) and (g) are protected by being converted to acetals and the selective oxidation of (g) to acrylic acid is carried out with silver oxide.

24. An aldehyde is oxidized more readily than an alcohol and therefore good yields of the aldehyde can be obtained only by removing it as it is formed. This is ordinarily done by distilling off a low-boiling aldehyde from the reaction mixture. A high-boiling aldehyde is readily oxidizable under these conditions and, besides, the difference in the boiling points of an alcohol and an aldehyde decreases with increasing carbon-chain length.

25. The oxidation by chromic anhydride in acetic acid or anhydride; chlorination to benzilidene chloride and acid hydrolysis.

26. Aluminium *tert*-butoxide reacts with the alcohol being oxidized to form trimethylcarbinol (incapable of oxidation under the reaction conditions) and an alcoholate (the equilibrium is shifted to the formation of the least acidic tertiary alcohol). Concerning the Oppenauer mechanism see A. R. Surrey, *Name Reactions in Organic Chemistry*, Academic Press, New York and London, 1961, page 177.

27. The oxidation is facilitated by enolization in an acidic medium; in a general case, ketone has two enols, which leads on oxidation to four acids, of course in different ratios (Popov's rule). Symmetrical ketones give one enol and hence two acids, and cyclic symmetrical ketones form one dibasic acid.

29. (a) (3) SeO_2 ; (4) O_3 or by oxidizing dihydrobenzoin (substance 2) by lead tetraacetate or periodic acid.

(b) (1) $\text{MnO}_2 + \text{H}_2\text{SO}_4$; (2) KMnO_4 ; heat.

(c) (4) From styrene; (5) acetophenone + $\text{SeO}_2 \rightarrow$ phenylglyoxal, which is to be oxidized by silver oxide to the acid.

(d) (1) Chromic anhydride; (3)-(5) from substance (1).

(e) (1-5) From cyclohexene (for (4): allyl bromination, followed by the action of CH_3COONa).

(f) (1) Careful oxidation by a Beckmann mixture; (2) addition of HCl to substance (1); (3) protection of the amino group by acylation.

(g) (1-3) From but-2-ene; (4) by condensation of acetaldehyde obtained by ozonolysis of but-2-ene.

30. Vigorous chlorination of ethyl alcohol and pouring of the reaction mixture into ethyl alcohol.

31. (a) KMnO_4 in the presence of magnesium nitrate; (b) a haloform reaction.

33. Acetal protection and oxidation by an alkaline solution of permanganate.

34. The Oppenauer reaction or the action of *tert*-butyl chromite.

35. Ozonolysis.

36. A Beckmann mixture or chromic anhydride in acetic acid.

37. Oxidation of methylcyclopentene by a Beckmann mixture; methylcyclopentene is obtained by dehydration of the carbinol resulting from the action of methylmagnesium iodide on cyclopentanone.

39. (a) The sodium derivative of cyclopentanonecarboxylic ester.

(b) Tri-*n*-propyl-*n*-butylmethane and tetra-*n*-propylethylene.

(c) Spiro(5,6)dodecan-7-ol.

(d) Acetaldehyde and glyoxylaldehyde.

(e) Phenylglycerine.

40. (a) (see D. Cram and G. Hammond, *Organic Chemistry*, page 559). (1) From benzoin by the action of amalgamated tin in hydrochloric acid; (2) from benzoin by the action of amalgamated sodium or from stilbene according to Wagner; (3) from benzoin by the action of amalgamated zinc or from

phenylbenzylcarbinol by dehydration; (4) from stilbene dibromide by the action of excess alcoholic alkali.

(b) See Problems 12 and 29 (c, 5).

(c) (1) Use must be made of acetal protection; (2) the Clemmensen reduction.

41. One convenient method is the action of amalgamated sodium on benzalacetone.

42. By ketonization of adipic acid.

43. By stereospecific oxidation of cyclohexene by potassium permanganate (H. Wagner) or by osmium tetroxide one can obtain *cis*-glycol; the *trans*-compound is obtained by using as an oxidizing agent a mixture of formic acid and hydrogen peroxide.

46. On careful oxidation only the primary alcoholic group (in butane-1,3-diol) is converted into an aldehyde which can easily be opened by qualitative reactions. α -Glycols are cleaved to carbonyl compounds (butane-2,3-diol to acetaldehyde) only by the action of lead tetraacetate or periodic acid.

47. Geometric isomers of but-2-ene.

48. *o*-Xylene since dimethylglyoxal could be obtained only from a molecule having vicinal methyl groups.

49. The hydrocarbon C_9H_{10} is *p*-methyl styrene. The hydrocarbon $C_{10}H_{12}$ may happen to be one of five *p*-disubstituted benzenes (among the possible radicals consider unsaturated radicals and a cyclic radical).

50. It is necessary to know the ratio of the reaction products, the molecular weight of the starting hydrocarbon or at least its composition.

51. This is obviously a cyclic hydrocarbon, but not necessarily the simplest 3-methylcyclohexene since 6,12-dimethylcyclododeca-1,7-diene and higher hydrocarbons of analogous structure will give on oxidation 2-methyladipic acid (see Introduction to this chapter).

52. An olefin that gives on oxidation only acetone is tetramethylethylene. But it could have been obtained not only by dehydration of dimethylisopropylcarbinol but also of methyl-*tert*-butylcarbinol (followed by retropinacolin rearrangement).

53. Isoprene or *gem*-dimethylallene.

54. This substance has one double bond and a keto group

and on ozonolysis forms acetaldehyde and pyrrolic aldehyde ($C_3H_4O_2$); it is obviously methyl propenyl ketone.

55. The starting substance is 3-methylcyclohexanone.

56. Since a diketone when subjected to the action of methylmagnesium iodide forms ditertiary glycol which dehydrates to a conjugated diene, it is obvious that the diketone is acetylacetone and the starting diene is 2,5-dimethylhepta-1,5-diene.

57. A substance of the composition $C_3H_4O_4$ which gives off carbon dioxide on heating may only be malonic acid, and hence $C_3H_4O_2$ is malonic aldehyde. The starting substance is symmetrical (on oxidation it forms only one product) and contains four hydroxyl groups. The formula $C_6H_{12}O_4$ leads one to assume the presence of either a double bond or a ring. The double bond would have been oxidized by the oxidants used and therefore the only answer possible is that the starting compound is a cyclic tetrahydric alcohol, namely, cyclohexane-1,2,4,5-tetraol, which, like other vicinal glycols, is cleaved by periodic acid or lead tetraacetate to give carbonyl compounds.

58. The substance $C_5H_8O_3$ is an ester and the acid when heated loses CO, i.e., it is α -keto acid. The positive haloform test for an alcohol points to the presence of the grouping

$\begin{array}{c} | \\ CH_3-CH-OH \end{array}$. These data permit one to assume that $C_5H_8O_3$ is ethyl pyruvate. Then $C_{10}H_{16}O_4$ is the diethyl ester of dimethylfumaric acid rather than of dimethylmaleic acid (acid B) because an anhydride forms difficultly from acid A. The *cis*-hydroxylation of a mixture of dimethylmaleic and dimethylfumaric acids must lead to a mixture of three possible stereoisomers (their isomerism is like the one in tartaric acids; see A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 1, page 389 and J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965).

59. Evidently the substance $C_6H_{12}O_6$ is one of aldohexoses. See A. N. Nesmeyanov and N. A. Nesmeyanov, vol. 1, page 440 and J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

60. The formation of the aldehyde $C_5H_{10}O$ enables one to

conclude that $C_5H_{12}O$ is a primary alcohol. The fact that two isomeric bromides are formed from the alcohol indicates that the reaction involves rearrangement, and the different attitude to alkalis and the formation of an alcohol isomeric to the starting one and also of the olefin C_5H_{10} , which is oxidizable to acetic acid (i.e., containing the fragment $CH_3-C=$), permit one to decide unambiguously that the starting substance is neopentyl alcohol.

CHAPTER 6

ORGANOMAGNESIUM COMPOUNDS

The wide availability and high reactivity of organomagnesium compounds have stimulated their wide use in synthetic, theoretical and analytical investigations.

In writing this chapter the authors did not try to cover all material concerning the structure and reactivity of organomagnesium compounds but only discussed the information that may be useful to the student in his study of a basic course and in his practical work in organic chemistry.

It is supposed that the previous topics—nucleophilic and radical substitution at the saturated carbon atom, condensation and tautomerism of carbonyl compounds, and also oxidation and reduction reactions—have already been worked up and the student has acquainted himself with the corresponding general concepts in textbooks.

Answers to questions and solutions of problems are given only in most complicated or fundamentally important cases.

Problems and Exercises

1. PREPARATION AND STRUCTURE OF ORGANOMAGNESIUM COMPOUNDS

The principal method for preparing organomagnesium compounds (Grignard reagents) is the interaction of alkyl or aryl halides with magnesium in diethyl ether. Other dialkyl ethers and also anisole, tetrahydrofuran, 1,2-dimethoxyethane and certain tertiary amines¹ are also used as solvents. The yield of Grignard reagents depends essentially on the nature of the halide used and the structure of the radical in

¹ Organomagnesium compounds can be prepared in the absence of a solvent as well.

the starting halogen derivative (see answers to Problems 9 and 10). Practically in all conversions organomagnesium compounds react as if they were of the formula RMgX ; their true structure however is still the subject of discussions (the corresponding material may be found in most textbooks). It should be kept in mind that very many functional groups react readily with organomagnesium compounds and that for this reason stable Grignard reagents cannot, as a rule, be prepared from halides containing functional groups. The preparation of Grignard reagents even from di- and trihalogen derivatives and also from halogen-substituted ethers and unsaturated halides is not always a sufficiently smooth process (see answers to Problems 7, 8, 12, and 14).

The preparation of some organomagnesium compounds from others, more available ones, by an exchange reaction is resorted to much more seldom. In this case the starting material (usually, a hydrocarbon) must contain a mobile hydrogen atom (see answers to Problems 12 and 16).

1. What is the effect of the nature of the halogen and of the structure of the radical in an alkyl halide on the course of the reaction by which an organomagnesium compound is prepared?

2. A Grignard reagent, whose properties are rather fully reflected by the formula RMgX , is a complex mixture of substances in equilibrium. What substances are these? What can be done to shift the equilibrium?

3. What is the effect of solvents on the reaction used for preparing Grignard reagents?

4. What requirements are set forth to starting materials, solvents and apparatus used for synthesis of organomagnesium compounds?

5. In preparing alkylmagnesium bromides and especially alkylmagnesium iodides the reaction should not be allowed to proceed too vigorously (the rapid addition of an alkyl halide to magnesium metal in ether should be avoided). What may happen if this condition is not observed?

6. Make a list of the ways for activating magnesium and outline their advantages and limitations.

7*. Write equations for reactions of the following dibromides with magnesium metal in ether: (a) 1,2-dibromoethane, 1,4-dibromobutane, 1,3-dibromopropane, *p*-dibromobenzene,

o-bromobenzyl bromide; (b) *p*-bromobenzyl bromide, diphenylchloromethane, 1,2-dibromobutane, methylene bromide, *o,o'*-bis-(bromomethyl)-diphenyl.

8*. What substances result from the reaction of the following compounds with an excess of magnesium metal in ether: 1-chloro-4-bromobenzene, 2-bromo-1-methoxybutane, 1-fluoro-2-bromobenzene, 1,4,5-tribromohexane?

9*. Arrange the following halogen derivatives in order of decreasing ease of interaction with magnesium: (a) methyl iodide, chlorobenzene, *n*-propyl chloride, neopentyl bromide; (b) allyl bromide, ethyl bromide, vinyl chloride, isopropyl chloride.

10*. Which of the following halogen derivatives gives an organomagnesium compound in the highest yield: (a) *n*-butyl bromide, *tert*-butyl iodide, isopropyl bromide; (b) benzyl chloride, benzyl iodide, chlorobenzene; (c) allyl bromide, methyl iodide, *sec*-butyl chloride? Explain your reasons.

11. The reactions in diethyl ether for preparing Grignard reagents are not necessarily conducted in a current of an inert gas, but with higher-boiling ethers, for example, with di-*n*-butyl ether, this is a necessary condition. Explain why.

12*. Under what conditions can the following organomagnesium compounds be obtained: phenylmagnesium chloride, allylmagnesium chloride, vinylmagnesium bromide, dibromodimagnesium acetylene, monobromomagnesium acetylene?

13. Which of the following substances can be used as solvents in preparing organomagnesium compounds: acetone, dioxane, water, anisole, tetrahydrofuran, dimethylformamide, 1,2-dimethoxyethane, diethylamine, pyridine, diethylene glycol, benzene? Explain your reasons. Compare all solvents that are suitable for the purpose (as to the field of application, the effect on the structure of an organomagnesium compound and its reactivity).

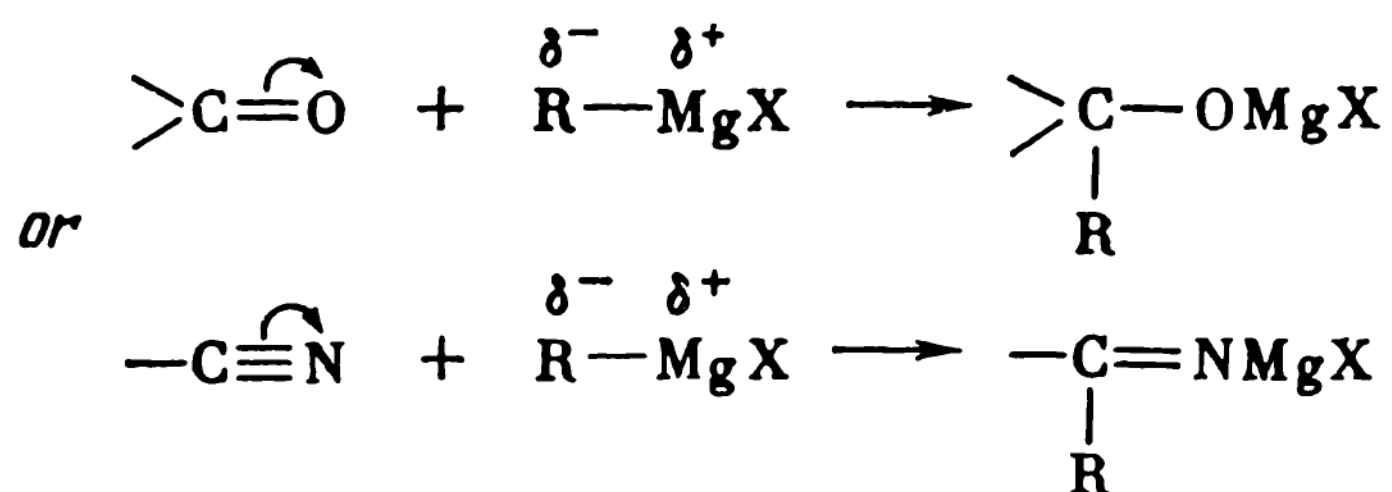
14*. What substances can result from the interaction of magnesium in ether with crotyl chloride (1-chlorobut-2-ene)?

15. Write an equation for the reaction of 3-chloro-2-methylprop-1-ene with magnesium under ordinary conditions.

16. Write equations for reactions of phenylacetylene, cyclopentadiene, indene, and fluorene (the last-named compound is heated in a high-boiling solvent, for example, in di-*n*-butyl ether) with ethylmagnesium bromide.

2. REACTIVITY OF ORGANOMAGNESIUM COMPOUNDS

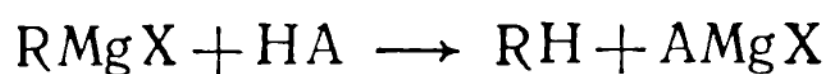
The reactivity of organomagnesium compounds is largely governed by the polarity of the carbon-magnesium bond and by the nature of magnesium itself. In an organomagnesium compound the carbon atom attached to magnesium bears a partial negative charge. For this reason Grignard reagents are capable of nucleophilic addition at multiple carbon-oxygen or carbon-nitrogen bonds; the alkyl (or aryl) group of a Grignard reagent is always moving to the carbon atom bearing such a multiple bond. For example,



The polarity of the carbon-magnesium bond in organomagnesium compounds is also responsible for the fact that they can function as nucleophiles in reactions of nucleophilic substitution. Examples are the reactions of replacement of an active halogen by a radical (see, for example, Problems 12, 14, and 15 and also Problems 50, 51, and 54) and of alkoxy groups in *ortho*-esters and acetals (Problem 53), the alkylation of Grignard reagents by dialkyl sulphates and alkylsulphonates (see Problem 69c and d) and also the reactions of opening of α - and β -oxide rings under the action of organomagnesium compounds (see, for example, Problem 57), their conversions into iodides on treatment with iodine (see Problem 56) and the exchange of halogens for radicals in halides of certain more electronegative elements than magnesium (for example, in PCl_3 , SiCl_4 , HgCl_2 , etc. (Problem 60).

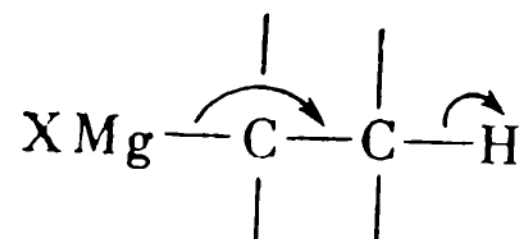
Besides the ability to act as nucleophiles in addition and substitution reactions, Grignard reagents are also capable of displaying basic properties owing to the polarity of the carbon-magnesium bond; they bind irreversibly (forming the corresponding hydrocarbons) mobile (i.e., readily splitt-

ing off as a proton) hydrogen atoms:



Examples are the reactions of organomagnesium compounds with acetylenes, cyclopentadienes, indene, and fluorene (Problems 12 and 16) and also with alcohols, acids, amines, and many other compounds. Such reactions are used for analytical purposes (the determination of active hydrogen by the Chugaev-Tserevitinov method; see Problems 61-63). It is because of their basic properties that Grignard reagents are decomposed by water (see Problem 64), which is used to incorporate deuterium (heavy water is taken) into an organic molecule (see Problems 96 and 97), and exert an enolizing effect (see Problems 21, 25, 26, 30, 32, 33, 65, 66, 67).

Another consequence of the presence of a partial negative charge on the carbon atom attached to magnesium is the relative ease of splitting off of the hydride ion from the carbon atom residing in the β -position relative to magnesium:



The transfer of the hydride ion to the carbon atom of a carbonyl compound results in the reduction of the latter to an alcohol. In certain cases (see Problems 17-22, 26, 29-31, 33) such reactions complicate the process of nucleophilic addition of organomagnesium compounds to ketones.

That organomagnesium compounds are capable, like magnesium halides, of exhibiting the properties of Lewis acids also affects their reactivity. Thus, for example, they cause, though to a small extent, the isomerization of α -oxides (see Problem 58), coordinate with carbonyl compounds at a stage preceding the formation of an alcohol (see Problems 19, 20, 21, 29) and form coordination compounds with ethers and tertiary amines.

A. Reactions with Aldehydes and Ketones

17. How would you account for the ability of organomagnesium compounds to act as nucleophilic agents, bases, and reducing agents (donors of the hydride ion)? Give concrete examples of the types of reaction indicated.

18*. The preparation of an alcohol from an aldehyde or a ketone is the process of reduction. Do you think that on addition of organomagnesium compounds at the carbonyl group there takes place its reduction?

19*. A normal reaction of RMgX with carbonyl compounds is the nucleophilic addition to the carbonyl group. The reduction of the latter to the corresponding hydroxyl group is considered a side process. What is common for these reactions? What factors make one of these reactions predominate (the concentration of a Grignard reagent, the reaction temperature, the order of mixing of reagents)?

20*. When branched ketones react with organomagnesium compounds, there may occur the reduction of a ketone to a secondary alcohol. What can be done to avoid this side reaction and to secure the corresponding tertiary alcohol in the highest yield? Give concrete examples.

21*. How are the reducing, enolizing, and condensing effects of organomagnesium compounds associated with the structure of reactants?

22*. What are the similarity and the difference between the mechanism of reduction of the carbonyl group with the aid of RMgX and the mechanism of reduction by magnesium alkoxides? What measures are taken to suppress these side reactions?

23*. What by-products can be formed in the preparation of diphenylcarbinol by the interaction of phenylmagnesium bromide with benzaldehyde? Does the yield of diphenylcarbinol depend on the order of addition of reagents?

24*. In the preparation of dimethylallylcarbinol by organomagnesium synthesis, acetone and allyl chloride are simultaneously added to magnesium which is under a layer of ether. Why is it necessary to carry out the reaction in such a way? What compound is the by-product of this reaction?

25*. It is known that the enolization of isobutyronone by the action of neopentylmagnesium chloride proceeds quantitatively, whereas *tert*-butylmagnesium causes enolization only by 60 per cent. How would you account for this difference?

26. What products result from the reactions of diisopropyl ketone with methylmagnesium bromide, neopentylmagnesium bromide, and isopropylmagnesium bromide? How could

you explain the difference in the course of these reactions?

27. Arrange the organomagnesium compounds within each of the following groups in order of increasing ease of their interaction with acetone: (a) phenylmagnesium bromide, ethylmagnesium iodide, *tert*-butylmagnesium chloride; (b) *p*-tolylmagnesium bromide, neopentylmagnesium bromide, methylmagnesium bromide; (c) cyclohexylmagnesium chloride, benzylmagnesium chloride, *tert*-amylmagnesium chloride.

28*. What will result from the treatment of an ethereal solution of a mixture of 1,2-dibromobutane and 1,4-dibromobutane with magnesium and then successively with excess acetone and water?

29*. When isopropylmagnesium bromide is added to certain ketones, along with the formation of a tertiary alcohol a gas will evolve. Name the gas. Explain the mechanism of its formation. What could be done to avoid side reactions leading to the evolution of the gas?

30. What is the principal route of the following reactions: (a) diisopropyl ketone with isopropylmagnesium bromide and methylmagnesium bromide; (b) phenyl benzyl ketone with neopentylmagnesium bromide and methylmagnesium bromide? How would you account for the difference in the course of the reaction in each case?

31*. When 2-methylbutan-1-ol is prepared from *sec*-butylmagnesium bromide and paraform, there will be formed, as by-products, methyl alcohol and di-*sec*-butylcarbinol (as a result of the hydrolysis of the reaction mixture). Explain this fact.

32. Write the schemes of principal and side reactions for organomagnesium syntheses involving the following pairs of compounds: (a) 2-magnesiumiodobutane and acetaldehyde; (b) phenylmagnesium bromide and benzaldehyde; (c) isobutylmagnesium bromide and benzophenone; (d) isopropylmagnesium bromide and 2,2-dimethylbutan-3-one; (e) propylmagnesium bromide and diisobutyl ketone; (f) hept-3-en-5-one and ethylmagnesium bromide; (g) acetophenone and *n*-propylmagnesium bromide; (h) 2-phenylpent-2-en-4-one and ethylmagnesium bromide; (i) acetophenone and isopropylmagnesium bromide.

33. Write equations for the reactions of the following pairs of compounds and formulate the mechanisms of the corresponding conversions: (a) diisopropyl ketone and neopentylmagnesium bromide; (b) trimethylacetic aldehyde and *tert*-butylmagnesium chloride; (c) dicyclohexyl ketone and isopropylmagnesium bromide; (d) cyclohexanone and isopropylmagnesium chloride; (e) vinyl-*tert*-butyl ketone and butylmagnesium bromide; (f) cyclopentanone and isopropylmagnesium bromide; (g) orthoformate and isopropylmagnesium bromide; (h) cyclohex-1-enyl-isopropyl ketone and ethylmagnesium bromide.

34*. How does the route of the reaction of α , β -unsaturated aldehydes and ketones with alkylmagnesium halides depend on the structure of the reagents used?

35*. It is known that chalcones ($\text{Ar}-\overset{4}{\text{CH}}=\overset{3}{\text{CH}}-\overset{2}{\underset{\text{Ar}'}{\text{C}}}=\overset{1}{\text{O}}$)

can add on alkylmagnesium halides both in the 1,2- and in the 1,4-position. What compounds result from the hydrolysis of the product of the reaction between benzalacetophenone and ethylmagnesium bromide?

36*. The radical decomposition of RMgX can be caused, as shown by Kharasch, by small additions of cobaltous chloride. Write the principal products of the reaction between benzophenone and ethylmagnesium iodide in the presence of this salt.

37*. What is the course of the reaction of methylmagnesium bromide with the following compounds in ether in the presence of cuprous chloride or cobaltous chloride: (a) isophorone (3,5,5-trimethylcyclohex-2-en-1-one); (b) 2-methylpent-2-en-1-one; (c) 2,4-dimethylhex-4-en-3-one; (d) 1,3-diphenylprop-1-en-3-one; (e) 1-phenylbut-2-en-1-one; (f) 3-methylcyclopent-2-en-1-one.

B. Reactions with Acid Derivatives and Carbon Dioxide

38*. Why can ketones be obtained from carboxylic acid chlorides and anhydrides in the case of the reverse addition of reagents (addition of organomagnesium compound) and why can they not be secured from esters?

39*. What is the course of the reactions of ethylmagnesium bromide with propionic and butyric acid chlorides? Will the route of the reaction change if, for example, in the first case the order of addition of reagents is reversed and the reaction is carried out at -70°C ?

40*. Which of the compounds in each of the following groups reacts faster with alkylmagnesium halide and why?

(a) diethyl ketone, propionyl chloride, propionaldehyde, propionic anhydride; (b) butyryl chloride, butyronitrile, di-*n*-propyl ketone; (c) acetyl chloride, acetone, ethylacetate; (d) benzamide, benzaldehyde, benzoyl chloride; (e) phenyltrichloromethyl ketone, acetophenone, benzophenone?

41*. 1,4-Dibromobutane is added to an excess of magnesium in ether; the ethereal solution of the resulting compound is treated with an equimolecular amount of ethylacetate and then with water. Write the equations of the corresponding reactions.

42*. Name the products of the reaction of ketene with an equimolecular amount and with an excess amount of phenylmagnesium bromide.

43*. Write the equations of the reactions of propionic anhydride with an equimolecular amount of phenylmagnesium bromide at -75°C and with its excess at room temperature.

44. Suggest the most expedient method of preparing 9-acetylphenanthrene from 9-cyanophenanthrene and compare it with other possible methods.

45. Write the equations of the reactions of an excess of ethylmagnesium bromide with diethyl carbonate, ethyl formate, and butyrolactone.

46*. How would you account for the fact that, in distinction to esters, the amides of carboxylic acids do not give tertiary alcohols on treatment with an excess of an organomagnesium compound and subsequent hydrolysis?

47. For synthesis of ketones via organomagnesium compounds use may be made of the amides and also of *N,N*-dimethylamides of carboxylic acids. Compare the advantages and limitations of the two methods.

48*. In the synthesis of carboxylic acids by the Grignard reaction, the ethereal solution of an organomagnesium compound is poured on dry ice. When solid carbon dioxide is added to a solution of an organomagnesium compound and

even more so when carbon dioxide gas is passed through this solution, lower yields of carboxylic acids are obtained. How can this fact be accounted for?

49*. Under what conditions can vinylacetic acid be secured from allyl chloride and acrylic acid from vinyl bromide by organomagnesium synthesis?

C. Reactions of Nucleophilic Substitution

50*. Which of the following alkyl and aryl halides reacts with ethylmagnesium bromide: benzyl iodide, ω -chlorostyrene, 3-chloro-2-methylprop-1-ene, chlorobenzene, bromomesitylene?

51*. When allyl chloride, 3-chloro-2-methylprop-1-ene, and 4-chloro-2,4-dimethylpent-2-ene react with organomagnesium compounds, individual products are formed (what products?). But if 2-chlorohex-3-ene is used as a second component in organomagnesium synthesis, there will result a mixture of products (what products?). Explain this phenomenon.

52*. What compound will result if methylmagnesium iodide is boiled in anisole and the reaction mixture treated with acidulated water?

53*. How do alkylmagnesium halides react with acetals, ketals and *ortho*-esters? Does the course of the reaction depend on the conditions under which it is carried out and how?

54*. How can hex-1-ene be obtained from vinyl butyl ether by a three-stage synthesis?

55*. The content of an organomagnesium compound in ethereal solution is determined by treating this solution with an excess of iodine and titrating this excess iodine with thio-sulphate. What reaction will take place?

56*. Suggest the most expedient method of converting the following halides into iodides: bromobenzene, neopentyl chloride, *p*-bromotoluene, chlorocyclohexane.

57*. How can primary alcohols be made by organomagnesium synthesis without using formaldehyde?

58*. A Grignard reagent is decomposed even by weak acids and is therefore considered a strong base. At the same time, under the influence of a Grignard reagent there sometimes occur reactions (for example, the isomerization of ethylene

oxide) which are induced by acids. How would you account for this phenomenon?

59*. Benzylmagnesium chloride, magnesiumbromomesitylene and 4-methylbenzylmagnesium bromide are heated in ethereal solution with diethyl sulphate, dimethyl sulphate and *n*-butyl *p*-toluenesulphonate, respectively. Write the equations of all the reactions indicated.

60*. Write equations for the reactions of phosphorus trichloride, mercuric chloride and zinc chloride with an equimolecular and an excess amount of phenylmagnesium bromide.

D. Reactions with Compounds Containing Mobile Hydrogen Atoms¹

61. How is active hydrogen determined according to Chugaev and Tserevitinov? What is the principle on which the method is based?

62. In the determination of active hydrogen by the Chugaev-Tserevitinov method a portion of a substance was taken, weighing 0.0360 g and consisting of carbon, hydrogen, and oxygen, and having a molecular weight of about 70. There was isolated 21.5 ml of methane (recalculated for normal conditions). How many active hydrogen atoms are contained in the substance being analysed? What might be the structure of this substance?

63. To determine the composition of a mixture obtained in the course of the synthesis of diethyl ether by the action of sulphuric acid on ethyl alcohol, use was made of the Chugaev-Tserevitinov method. A portion of the mixture weighing 0.9280 g was taken and 13.2 ml of methane was collected (under normal conditions). What is the percentage content of unreacted ethyl alcohol in the mixture?

64*. Methyl *p*-tolyl ether, which contains O¹⁸ and is therefore of great value, was accidentally mixed with iodobenzene. Name the most expedient method of isolating the ether from the mixture (the boiling points of both substances are practically the same and the amount of the mixture involved is too large for preparative chromatography to be employed).

¹ See also Problems 21, 25, 26, 30, 32, 33 which deal with the enolization of ketones.

65*. In some cases enolization taking place under the influence of RMgX is used for preparing special reagents. Thus, the interaction of phenylacetic acid with two moles of isopropylmagnesium chloride results in the formation of the Ivanov reagent, which is one of polyfunctional organomagnesium compounds. How would you prepare phenylmalonic acid by using this reagent? What other methods of preparing phenylmalonic acid without the use of RMgX would you suggest? Write equations for the reactions of the Ivanov reagent with acetone, ethylene oxide, and iodine.

66*. To an ethereal solution of acetoacetic ester is added an equimolecular amount of an ethereal solution of methylmagnesium iodide. The reaction mixture is then treated with iodine. Write the equations of the corresponding reactions.

67*. How would you account for the formation of α , γ -diphenyl- β -ketobutyronitrile by the action of methylmagnesium iodide on an excess of phenylacetonitrile and by subsequent hydrolysis?

68. In pentafluorobenzene, the only hydrogen atom in the benzene ring acquires acidic properties under the influence of electronegative fluorine atoms. What compound results from the successive treatment of pentafluorobenzene with ethylmagnesium bromide, carbonic acid and dilute hydrochloric acid?

E. Interaction of Organomagnesium Compounds with Various Reagents¹

69. Write equations for the reactions of equimolecular amounts of alkylmagnesium halide RMgX ($\text{X} = \text{Cl}, \text{Br}, \text{and I}$) with the following organic reagents: (a) benzoic anhydride, ethylamine, 2-chloropent-3-ene*, acetonitrile; (b) ethyl formate, phenylacetylene, allyl chloride, acetylene; (c) acetamide, acetoacetic ester*, cyclopentadiene, dimethyl sulphate*; (d) acetone, succinimide, 4-bromopent-2-ene*, benzonitrile, diethyl sulphate*; (e) *p*-cresol, butyronitrile, diethyl

¹ After the student has firmly mastered the previous material he will be able to answer easily most of the questions in this section. Problems that may be difficult to solve are marked with an asterisk and supplied with answers.

carbonate*; (f) propionic aldehyde, phenyl formate, 1-chlorobut-2-ene*, adiponitrile*; (g) orthoformic ester, acetanilide, cyclohexane-1,3-dione*, propylene oxide; (h) N-methylaniline, chloromethyl ethyl ether*, benzyl mercaptan, chlorocarbonic ester*; (i) ethylene oxide, paraform, isopropyl acetylene, phthalic anhydride*; (j) ethylenebromohydrin, malonic dinitrile*, methyl-*tert*-butylamine, phthalimide; (k) fluorene, butyryl chloride, hept-1-yne, α,β -dibromoethyl-*n*-butyl ether*; (l) benzonitrile, acetylacetone*, 3-bromobut-1-ene*, cyclobutanone; (m) calcium acetate*, *m*-cresol, 3-bromo-2-methylprop-1-ene*, triacetylmethane*; (n) *p*-chlorophenol, 2-bromo-2-methylbut-3-ene, chloroacetic aldehyde*, butyrolactone.

70. Write equations for the reactions of an alkylmagnesium halide RMgX ($\text{X} = \text{Cl}, \text{Br}, \text{and I}$) taken in excess with the following reagents: (a) acetylene, octane-2,7-dione, benzoic acid, butyl acetate; (b) propionic anhydride, butane-2,3-dione*, propionyl chloride, orthoformic ester*; (c) acetamide, phosgene*, salicylaldehyde, orthocarbonate*; (d) ethyl β -benzoylpropionate*, levulinic acid*, chlorocarbonate*, acetaldehyde diethyl acetal*; (e) benzoin*, diethylcarbonate*, di-*tert*-butyl ketone*, malonic ester*; (f) phenylhydrazine*, formic acid, valerolactone, diethyl succinate*.

71*. Write equations for the reactions of an equimolecular amount of an alkylmagnesium halide RMgX ($\text{X} = \text{Cl}, \text{Br}, \text{and I}$) in ether with the following reagents: (a) bromine, cupric bromide, ethereal solution of ammonia, oxygen; (b) sulphur, iodine, phosphorus trichloride, mercuric chloride; (c) dry gaseous hydrogen bromide, silver bromide, cadmium chloride, cobaltous chloride; (d) dioxane, dilute solution of hydrochloric acid, heavy water, cobaltous bromide, trideuteroammonia.

72*. Write equations for the reactions of an excess amount of an alkylmagnesium halide with the following inorganic reagents: ammonia, bismuth trichloride, mercuric chloride, cadmium chloride, silicon tetrachloride, ferric bromide.

73*. What will result from the action of the following compounds on dibromodimagnesium acetylene (the Iotsich complex): (a) allyl chloride (2 moles); (b) paraform (1 mole and 2 moles); (c) acetonitrile (1 mole and 2 moles); (d) acetylene (1 mole)?

74. An organomagnesium compound is made from α -chlorostyrene (under what conditions?). How will it react with carbon dioxide, water, and acetaldehyde?

F. Application of the Grignard Reaction for Determination of the Structure of Organic Compounds

75*. When ketone $C_5H_{10}O$ (I) reacts with ethylmagnesium bromide and the resulting carbinol is dehydrated, it is converted into alkene (II), which on ozonization gives diethyl ketone and acetaldehyde. Suggest structures for compounds I and II.

76*. When compound A is added to an ethereal solution of organomagnesium iodide, methane is liberated and compound B is formed. The treatment of compound A with a sulphuric acid solution of mercuric sulphate leads to 2,2-dimethylbutan-3-one, which when allowed to react with B and on subsequent hydrolysis with water is converted to compound C. What are the structures of compounds A, B, and C?

77*. An organomagnesium compound was prepared from vinyl bromide (under what conditions?). When this compound was treated first with propylene oxide and then with water, compound A was obtained, which was allowed to react with propionic anhydride for synthesis of compound B. What are the structures of compounds A and B?

78*. The reaction of an organomagnesium halide with diethyl ketone led to a tertiary alcohol, which when subjected to dehydration and subsequent catalytic hydrogenation gave 3-ethylpentane. What is the structure of the starting organomagnesium compound?

79*. Compound A reacts with methylmagnesium bromide to give a tertiary alcohol. When compound A is treated with phosphorus pentachloride and then heated with hydrogen iodide, *n*-butane is formed. Suggest a structure for compound A.

80*. Compound A when subjected to alkali hydrolysis with the reaction mixture being then acidified is converted to acetic acid. The addition of A to an ethereal solution of methylmagnesium bromide and subsequent hydrolysis result in the formation of acetone. Suggest the structure for compound A.

81*. When compound A is added to an excess of an ethereal solution of methylmagnesium bromide, methane is liberated and when the reaction mixture is hydrolysed there is formed dimethyl ethylcarbinol. Determine the structure of compound A.

3. APPLICATION OF ORGANOMAGNESIUM COMPOUNDS FOR SYNTHETIC PURPOSES

To solve the synthetic problems of this section it is necessary to work up thoroughly the material of the previous chapters and have a good knowledge of the methods of preparation and the reactivity of organomagnesium compounds (Sections 1 and 2 of this chapter).

82. Prepare the following compounds by using only inorganic reagents:

(a)* hept-2-ynoic and 2,5-dimethyladipic acids from propylene;

(b)* 2-methylpentan-2-ol and heptan-4-one from propylene;

(c)* acetylenedicarboxylic acid and 2,5-dimethylhex-3-yne-2,5-diol from acetylene;

(d)* 3-methylheptan-3-ol and 3-methylhept-4-yn-3-ol from but-1-ene;

(e) stilbene, dibenzylphenylcarbinol, phenyl benzyl ketone, tribenzylcarbinol, dibenzyl ketone, dibenzylacetic acid*, phenylacetic acid, 1,2-diphenylethanol, 1,2-diphenylethane, phenylbenzylcarbinol from toluene;

(f)* dimethylethylcarbinol and 2,5-dimethylhex-3-yne-2,5-diol from acetylene;

(g)* phenylacetone, dimethylbenzylcarbinol, methylethylbenzylcarbinol, 2,5-dimethyl-1,6-diphenylhex-3-yne-2,5-diol from toluene and acetylene;

(h) isopropyl alcohol*, diisopropylacetic acid*, 4-methylpenta-1,3-diene, isobutyric acid, *tert*-butyl alcohol, hexa-1,5-diene, dimethylallylcarbinol*, diisopropyl ketone, di-*n*-propyl ketone from methanol;

(i) isoamyl and *tert*-amyl* alcohols, triethylcarbinol*, methylethylacetic acid, butan-1-ol*, methyl ethyl ketone, propionic acid from ethanol;

(j) ethyldipropylcarbinol, hexa-1,5-diene, isobutyl alcohol*, ethyl-*n*-propyl ketone*, dimethylallylcarbinol, 2-methyl-4-ethylhept-1-en-4-ol* from propan-1-ol;

(k) propyl butyl ketone, methylethylacetic acid, di-*n*-butyl ketone*, tri-*n*-butylcarbinol*, *n*-butyl valerate from butan-1-ol;

(l)* isoamyl ester of 4-methylpent-2-ynoic acid from isoamyl alcohol;

(m) 2,5-dimethylhexa-1,5-diene from isobutyl alcohol;

(n) tricyclohexylcarbinol, dicyclohexyl ketone*, 1,6-dicyclohexylhexane-1,6-diol*, dicyclohexylacetic acid* from cyclohexanol;

(o)* propionaldehyde, isobutyraldehyde acetal, 2-ethylbutan-1-al from orthoformic ester;

(p) triphenylcarbinol and benzophenone from bromobenzene;

(q) diethylacetic acid and pentan-3-ol from ethyl formate;

(r)* 1-methylcyclopentan-1-ol from methyl alcohol and adipic acid;

(s) 2-methylpent-3-yn-2-ol*, but-2-yn-1-oic acid from acetylene;

(t) trimethylacetic (pivalic) acid and 2,5-dimethylhexa-1,5-diene from isobutylene.

83. Name at least two possible paths of one-stage synthesis of the following compounds via organomagnesium compounds. Discuss the advantages and limitations of each method:

(a) butan-2-ol, hexan-1-ol, 2-methylbutan-3-ol, 3-methylpentan-3-ol, ethyl butyl ketone, *tert*-amyl alcohol;

(b) benzylisopropylcarbinol, di-*sec*-butylcarbinol, 2-methylpentan-2-ol, methylisobutylcarbinol, triphenylcarbinol;

(c) 2,4-dimethylpentan-2-ol, pinacolin, 2,4-dimethylhexan-5-ol, 2,4-dimethylhexan-6-ol, 2,4-dimethylpentan-3-ol;

(d) phenylacetic acid, 2,3-dimethylbutan-2-ol, methyl benzyl ketone, β -phenylethyl alcohol, α -naphthoic acid;

(e) methylpropylphenylcarbinol, isoamyl alcohol, butyraldehyde, benzhydrol, methyl isopropyl ketone;

(f) pentan-3-ol, methylphenylacetic acid, β -phenylpropionaldehyde.

84*. Give examples of synthesis of hydrocarbons—alkanes, alkenes and alkadienes — via organomagnesium compounds.

85*. Give examples of synthesis of organometallic compounds via organomagnesium compounds.

86. Give and discuss on concrete examples the possible paths of synthesis of the following compounds via organomagnesium compounds: aldehydes, ketones, primary alcohols, diols, and thioalcohols.

87. Suggest the most rational way of synthesizing the following compounds (discuss and compare with other possible ways):

(a) 1-phenylhex-5-en-1-ol, 3,6-dimethyloctane-2,7-diol; 2-methylpentan-3-ol, decane-1,10-diol, octa-1,7-dien-4-ol;

(b) non-1-en-7-yn-5-ol, 2,3,4-trimethylhept-6-en-2-ol, 3,6-dimethyloctane-3,6-diol, methyldiphenylcarbinol, *n*-amyl alcohol;

(c) diethylacetic acid, triethylcarbinol, benzophenone, trimethylacetic acid, diisopropyl ketone;

(d) β -cyclohexylethyl alcohol, allylbenzene, cyclohexylcarbinol, ethyl isopropyl ketone, 2-phenylpentan-4-one;

(e) diethyl acetylenedicarboxylate, 3-methyl-1-phenylpent-1-yn-3-ol, 2,7-dimethyloctane-2,7-diol, 5-phenylpentan-4-on-1-oic acid;

(f) oct-3-yn-2-one, propenylbenzene, butyne-2-dial tetraethylacetal, hex-1-en-3-ol, oct-2-yn-1-ol;

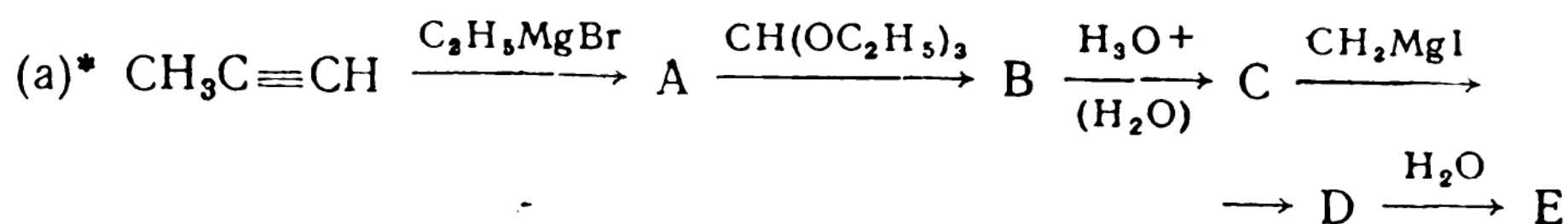
(g) phenylpropargylic aldehyde, methylethylisopropylcarbinol, *tert*-butylethylcarbinol, methylethylphenylcarbinol.

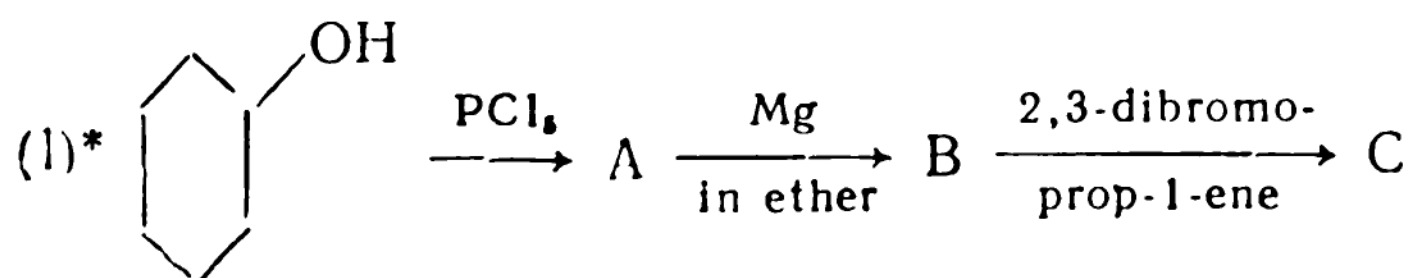
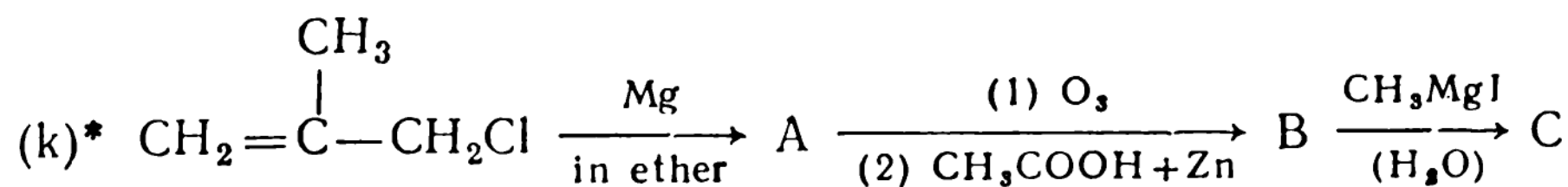
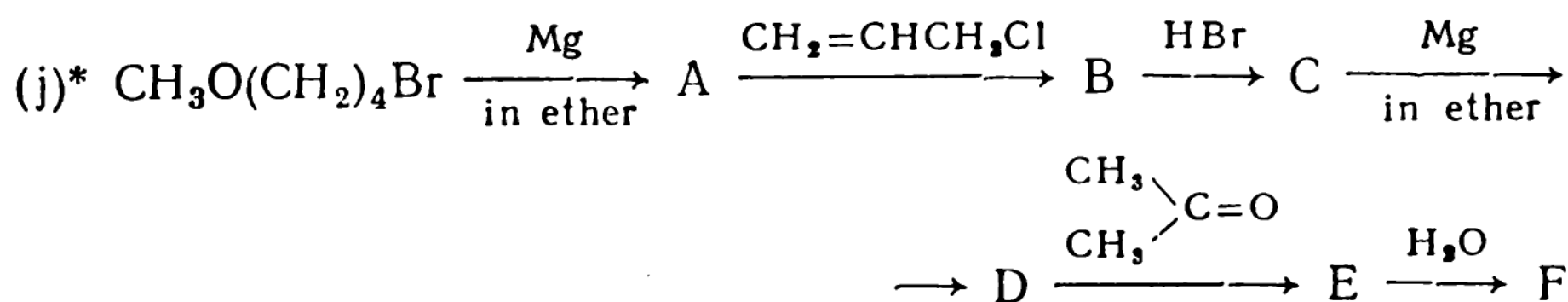
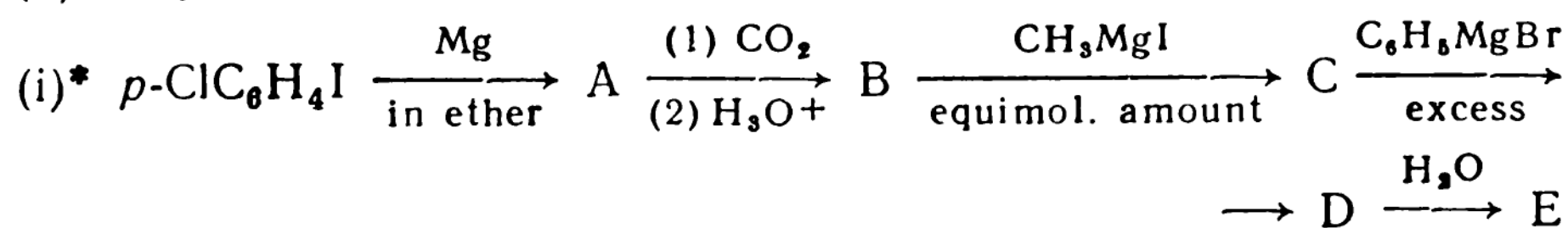
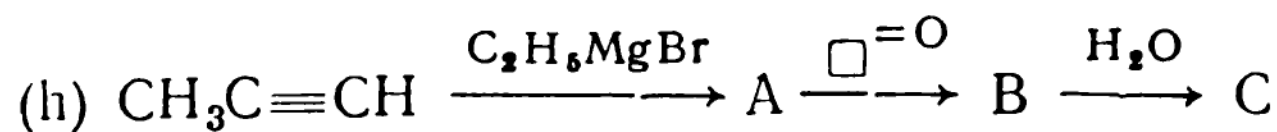
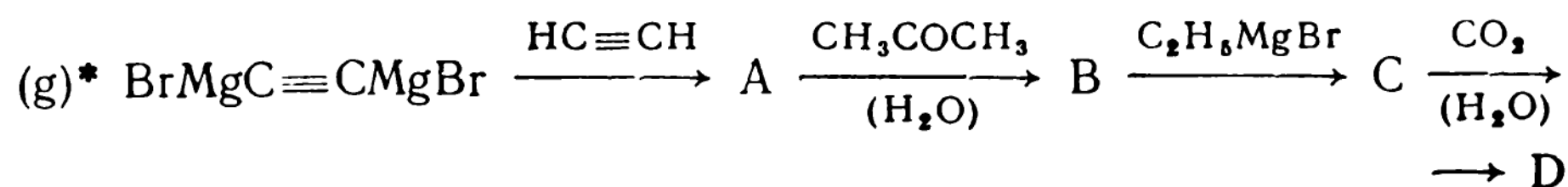
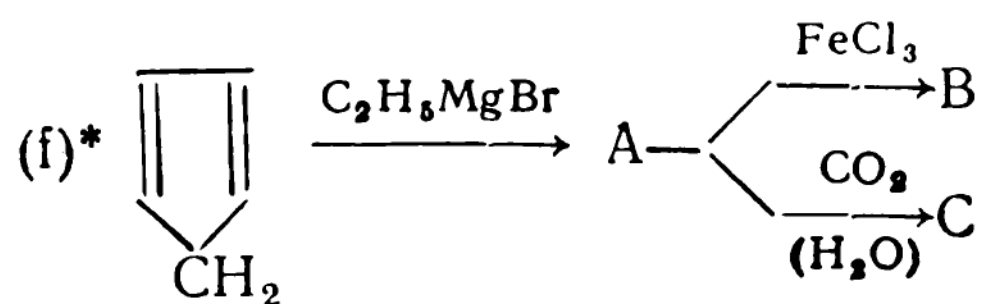
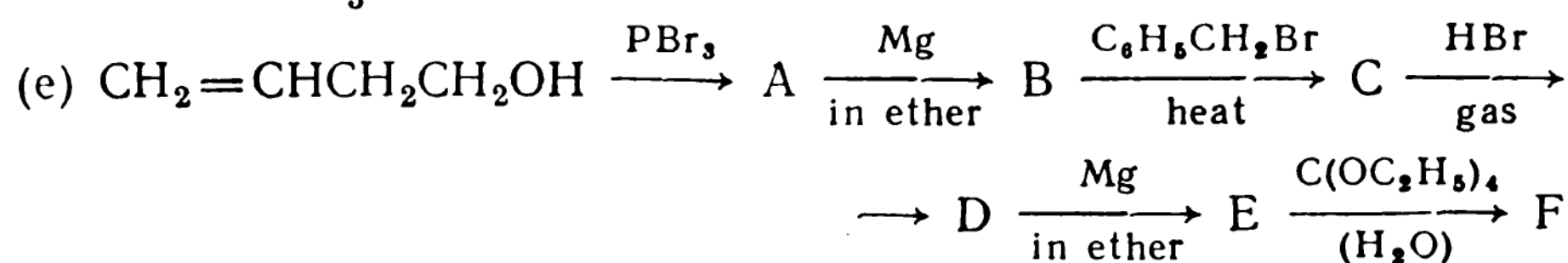
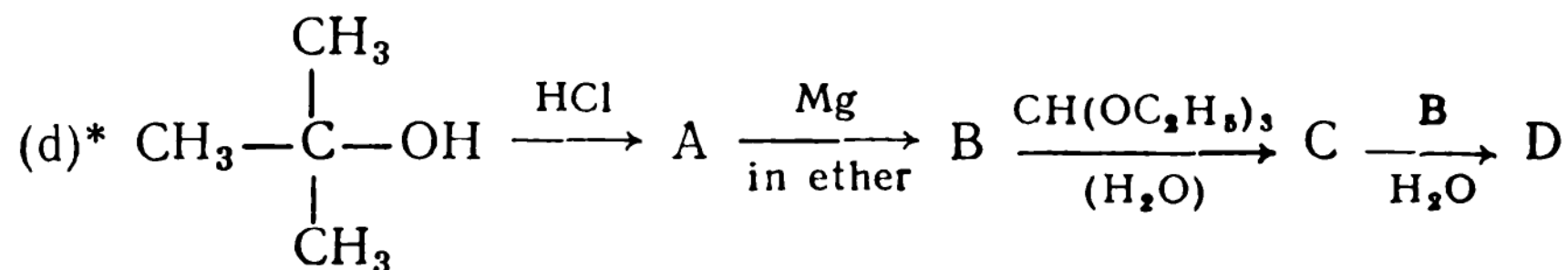
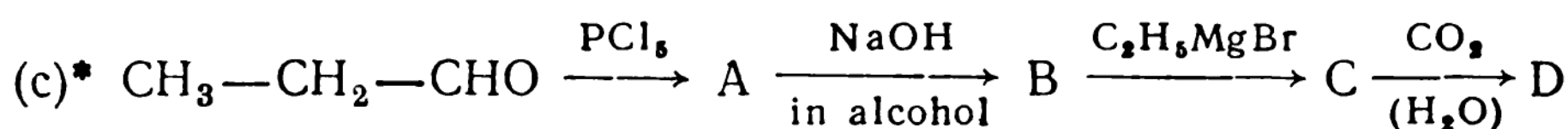
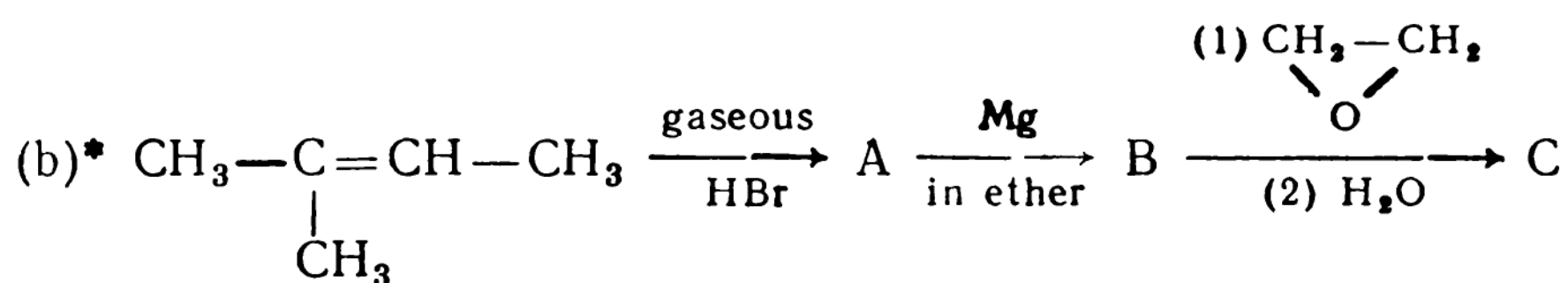
88*. Name the acetylene hydrocarbon from which but-2-yn-1-oic acid is most readily obtained.

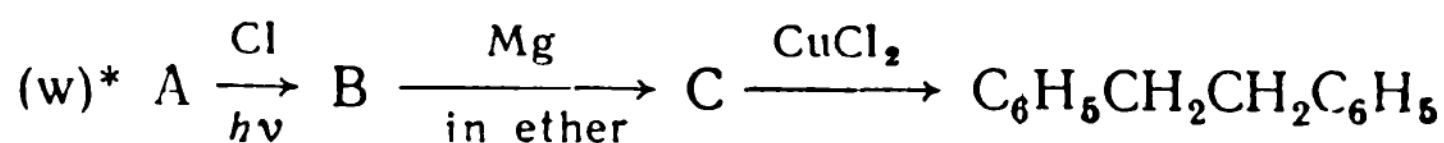
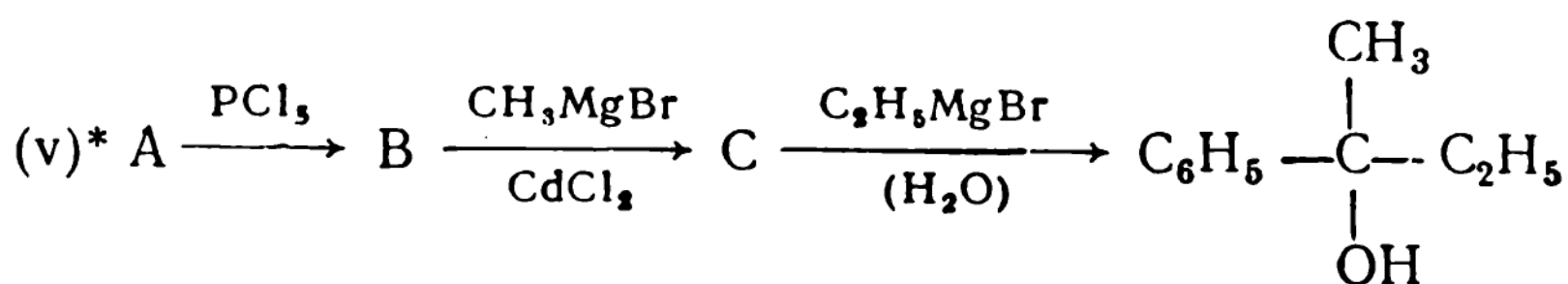
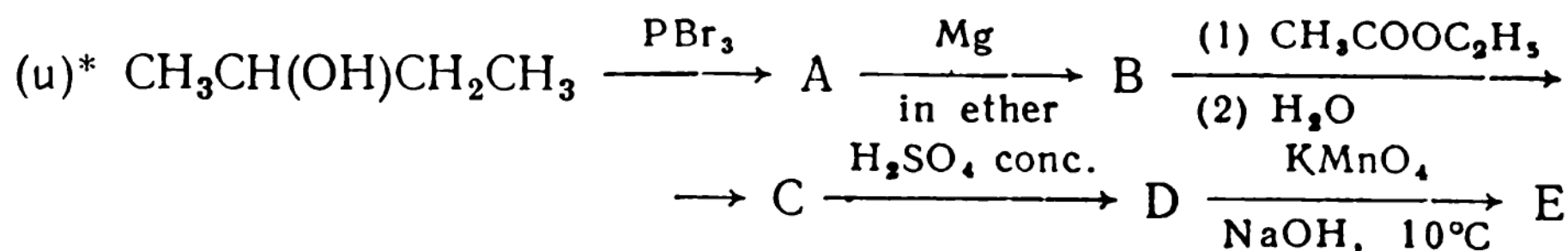
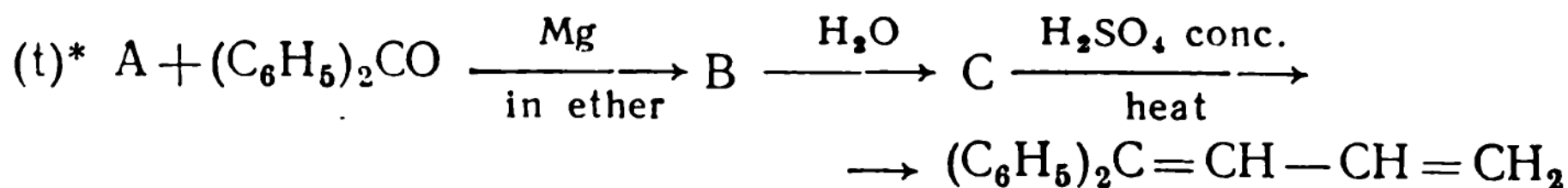
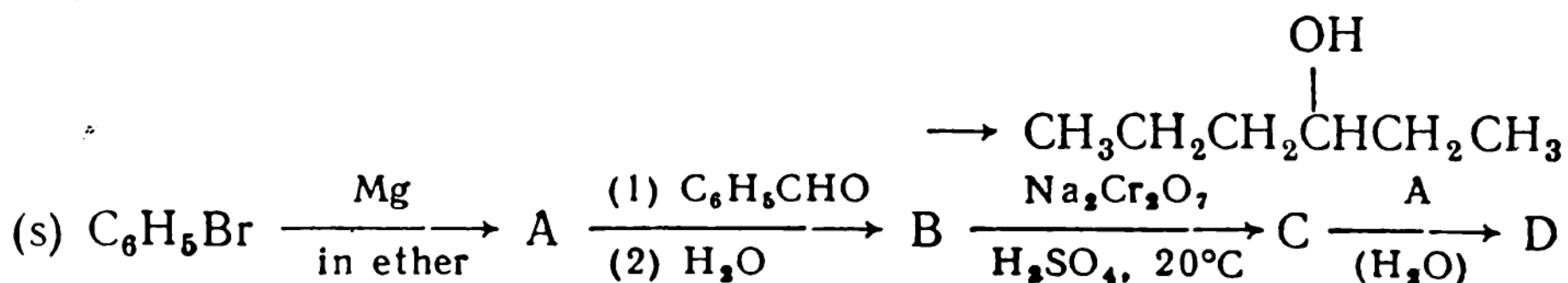
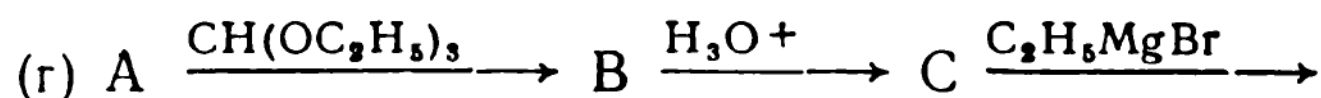
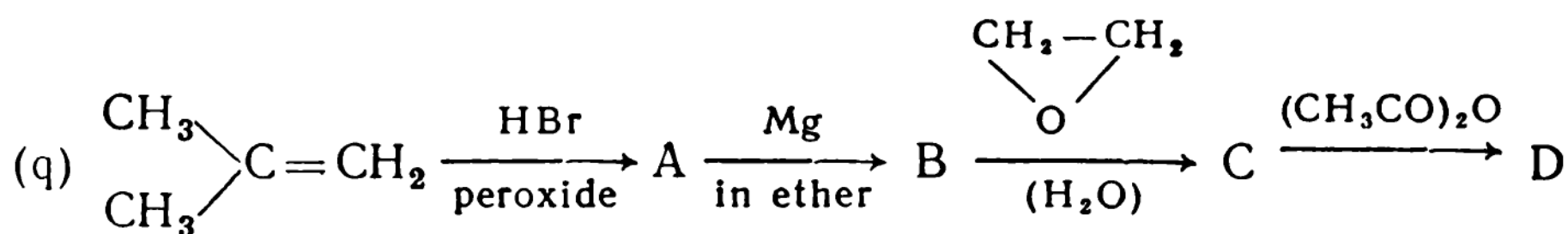
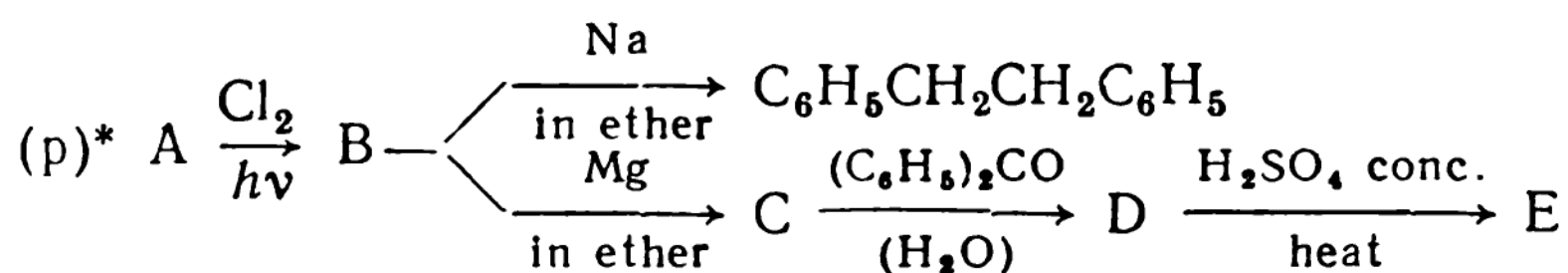
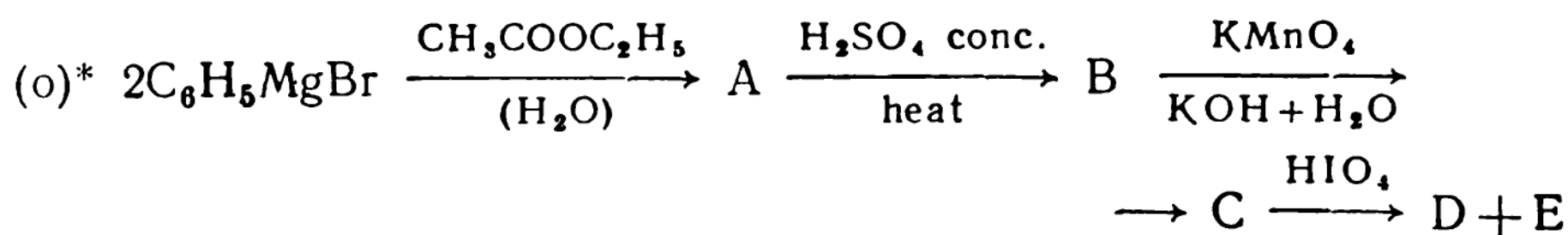
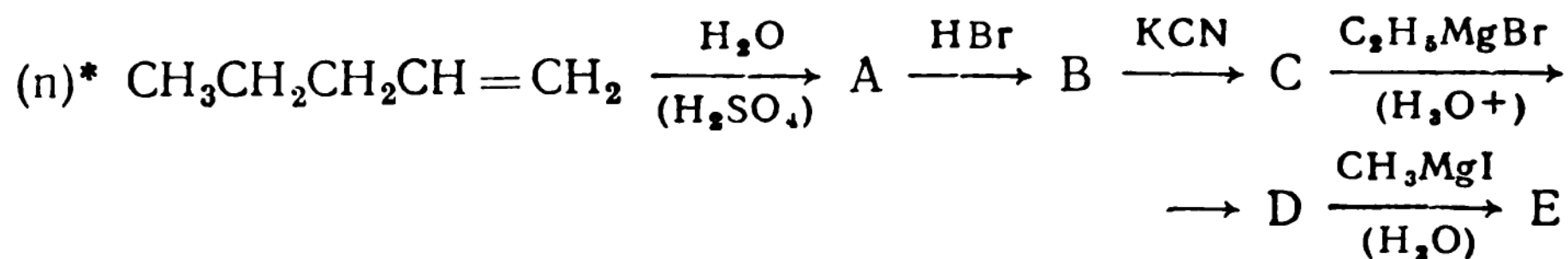
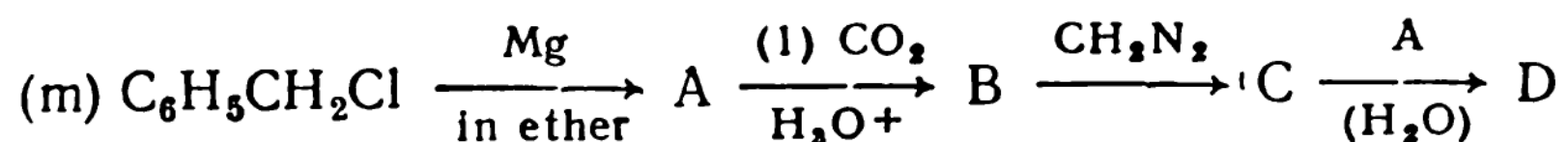
89. Outline all the possible ways of synthesizing *n*-amyl, β -phenylethyl and γ -phenylpropyl alcohols using organomagnesium compounds.

90. Accomplish syntheses of the following compounds from inorganic reagents only: *n*-butyl alcohol, methyldiisobutylcarbinol, methylpropylcarbinol, acetylenedicarboxylic acid, hexane-1,6-diol, 2,3-dimethylhexan-3-ol, 2,3,4-trimethylpentan-2-ol, dimethylisobutylcarbinol, 2,5-dimethylhex-3-yne-2,5-diol.

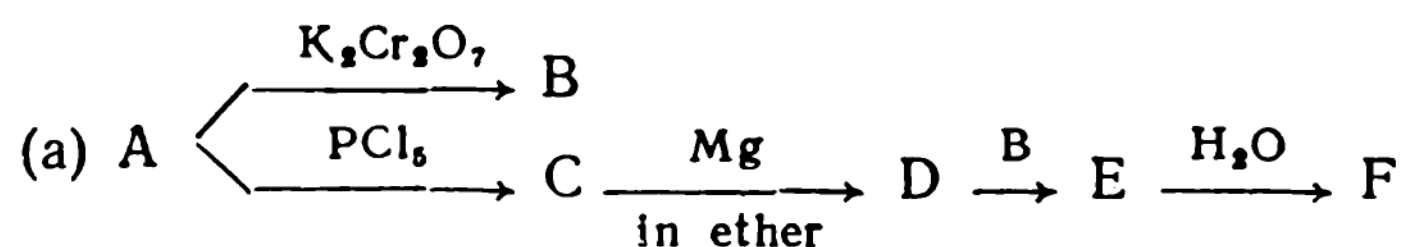
91. Decipher the schemes of the following conversions; write the formulas of the intermediates and final products of the reactions involved:



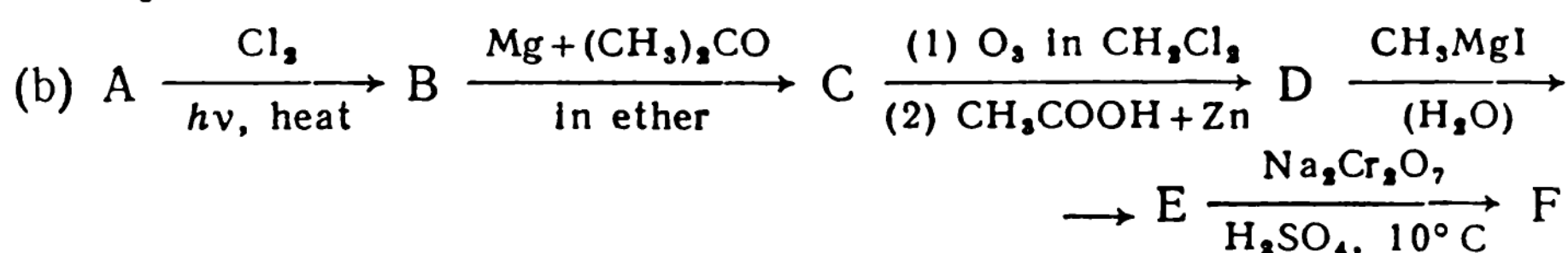




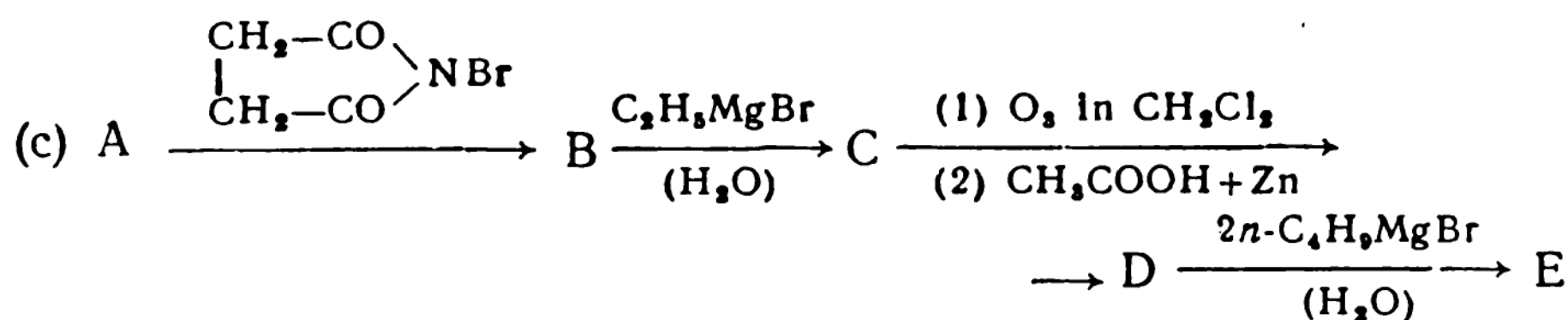
92. Write the scheme of the following conversions and name the intermediates and final products:



if $A = \text{sec-butyl alcohol, methylbutylcarbinol, methylisopropylcarbinol, ethylisopropylcarbinol, methyl-sec-butylcarbinol, pentan-2-ol;}$

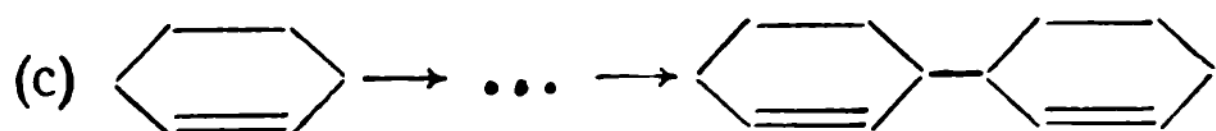
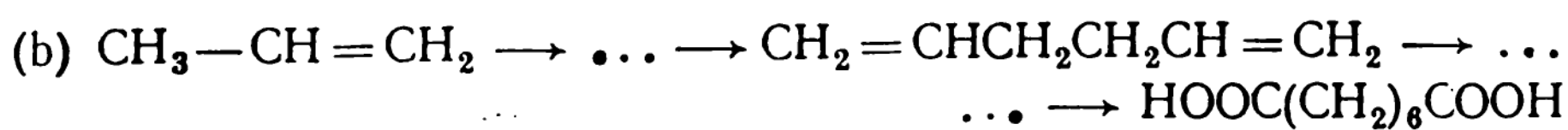
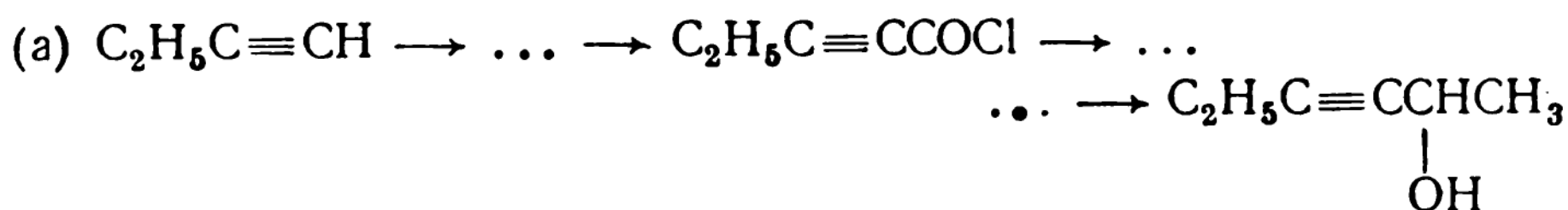


if $A = \text{propylene, isobutylene, 2,4-dimethylpent-2-ene, } \alpha\text{-methylstyrene;}$



where $A = \text{cyclopentene or cyclohexene.}$

93. Complete the schemes of the following conversions:



94. Using $CaC^{14}O_3$ and any organic and inorganic substances containing no tracer atoms, prepare, without loss of activity, the following compounds:

(a) butan-2-one ($3-C^{14}$)*, butan-2-one ($2-C^{14}$);

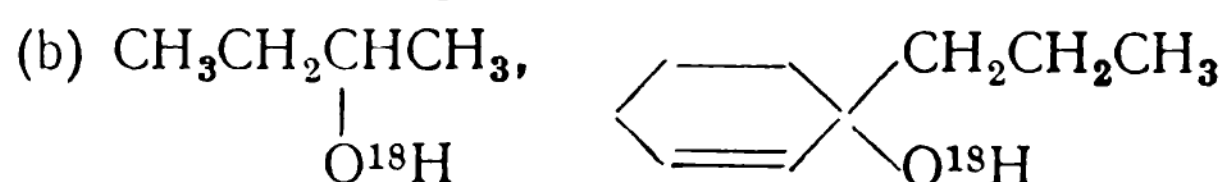
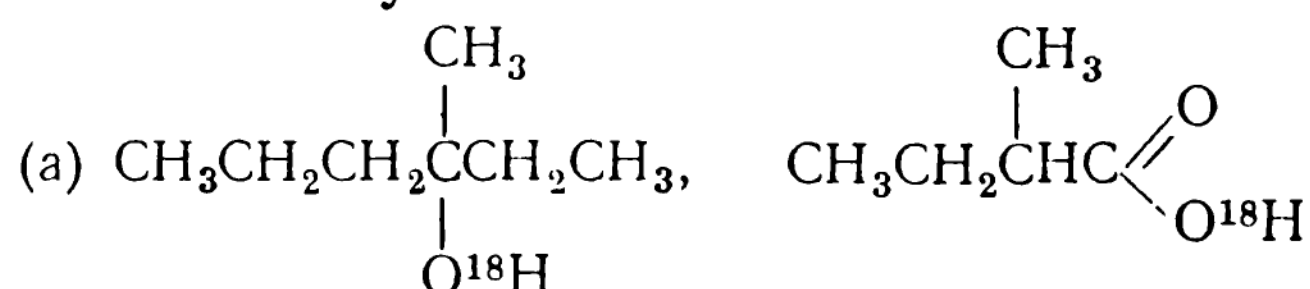
(b) 2-methylbutan-3-one ($2,3-C^{14}$), α -methylbutyric ($\alpha-C^{14}$) acid;

(c) β -phenylethyl ($\beta-C^{14}$) alcohol, pentan-2-one ($2,4-C^{14}$);

(d) 1-phenylpentan-1-one ($1,4-C^{14}$), 2,4-dimethylpentan-3-one ($2,4-C^{14}$);

- (e) 2-methylpentan-4-one (3-C¹⁴), pentan-3-one (2-C¹⁴);
 (f) styrene (α, β -C¹⁴)*, α -methylstyrene (α -C¹⁴);
 (g) pent-1-ene (5-C¹⁴), triphenylcarbinol (α -C¹⁴);
 (h) but-3-en-1-oic (1-C¹⁴) acid, isobutyric (α -C¹⁴) acid;
 (i) hexane-1,6-dioic (1,6-C¹⁴) acid, nona-1,8-dien-4-one (5,6-C¹⁴);
 (j)* phenoxyacetic acid C₆H₅OCH₂C¹⁴OOH.

95*. Synthesize the following compounds from substances that contain no tracer atoms and from H₂O¹⁸ with a minimal loss of activity:



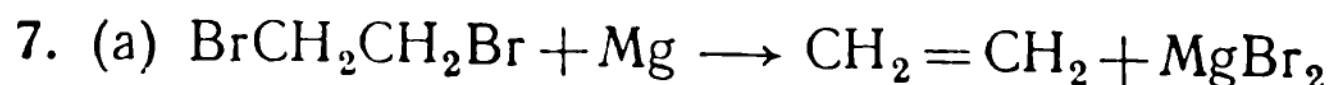
96. Using D₂O and substances that contain no tracer atoms, synthesize the following compounds:

- (a)* 5-deuteriopent-1-ene, 1,4-dideuterohexane;
 (b) 3-deutero-1-cyclohexylpropane, 4-deutero-1-phenylbutane;
 (c) 3-deutero-1-*p*-deuterophenylpropane*, 3-deuterobutan-2-ol.

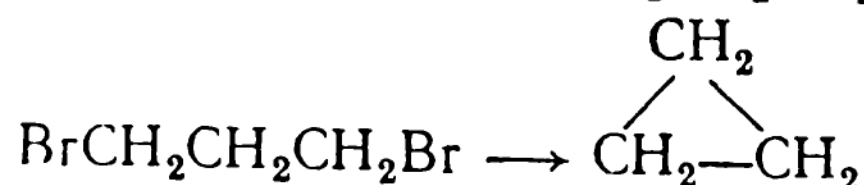
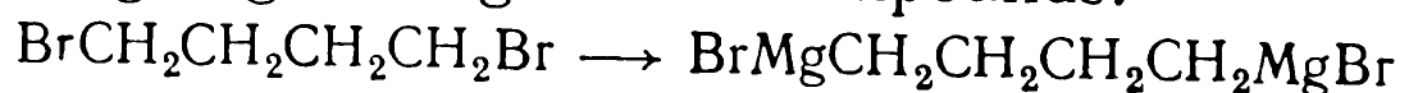
97*. Synthesize compounds that would contain simultaneously O¹⁸ and C¹⁴, and also D and O¹⁸, and D and C¹⁴ (CaC¹⁴O₃, D₂O, and H₂O¹⁸ are available):

- (a) CH₃C¹⁴H₂O¹⁸H;
 (b) DCH₂CH₂CH₂CH₂CH₂O¹⁸H;
 (c) $\text{CH}_3\overset{\text{O}^{18}\text{H}}{\text{CH}}\text{C}\equiv\text{C}-\text{C}^{14}\text{OOH}$

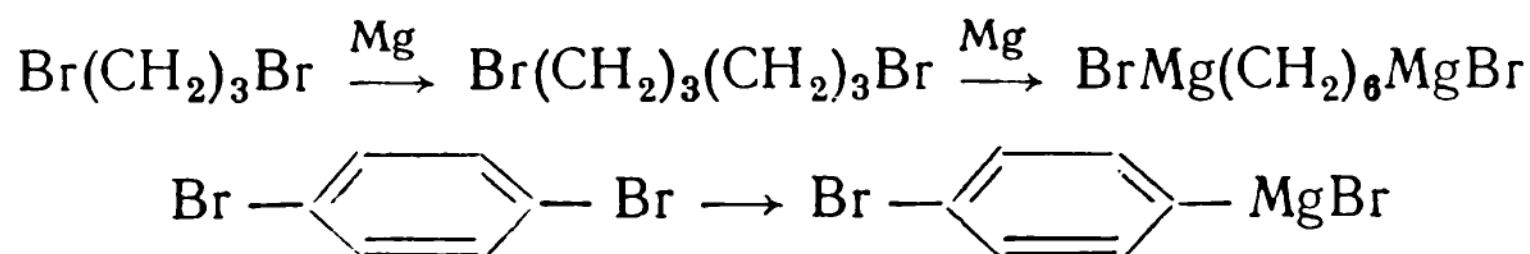
Answers



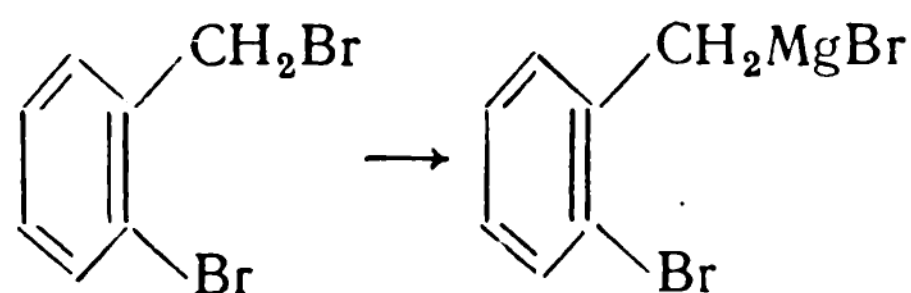
This reaction is occasionally used to activate magnesium in preparing organomagnesium compounds:



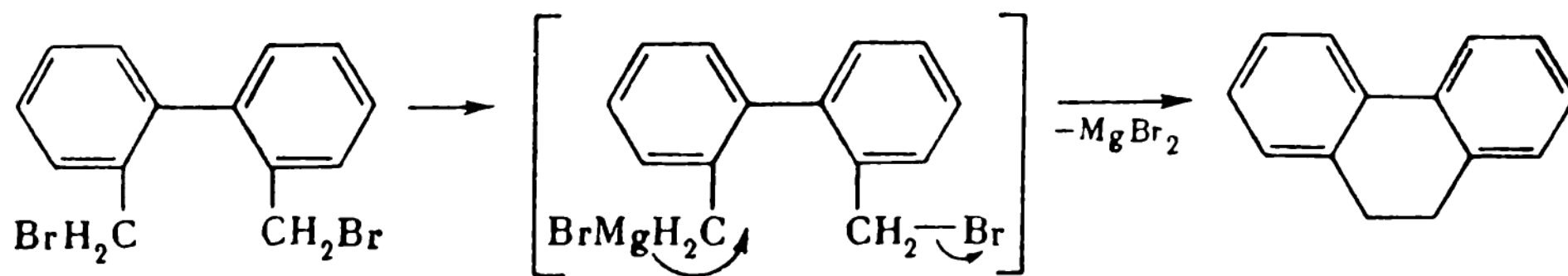
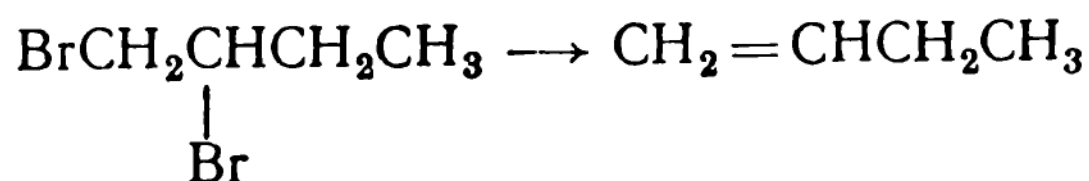
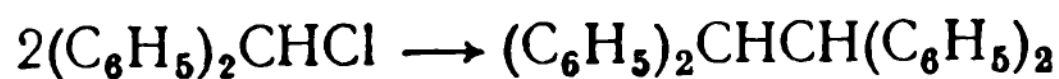
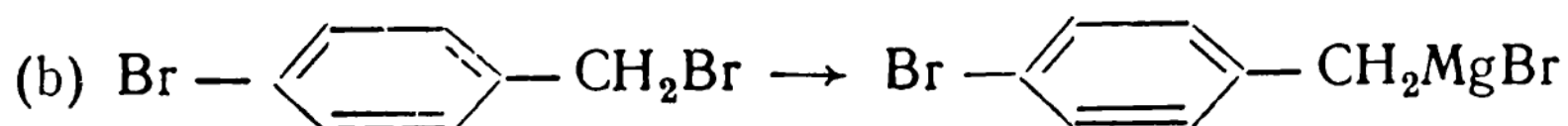
In the latter case there are formed, as by-products, small amounts of propylene and bis-magnesium bromide with six carbon atoms as a result of dimerization according to the scheme:



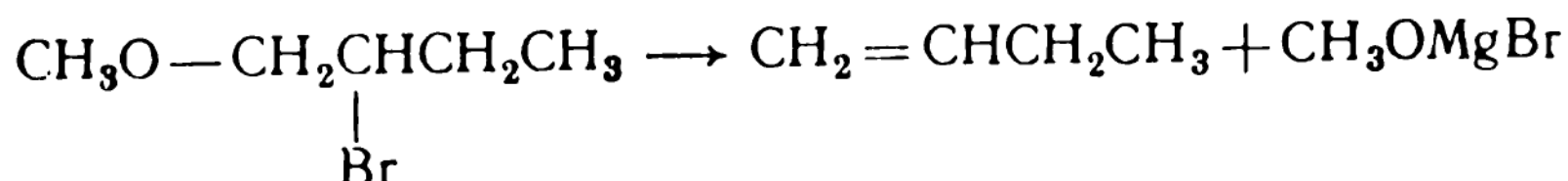
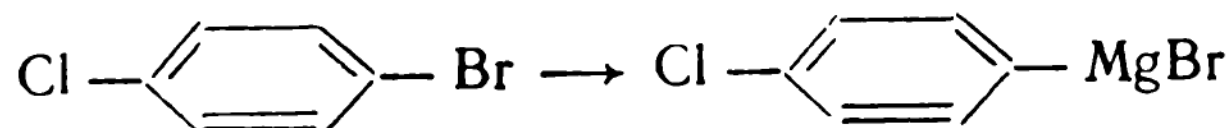
Bis-magnesiumbromoderivative can be obtained from *p*-di-bromobenzene only under special conditions:



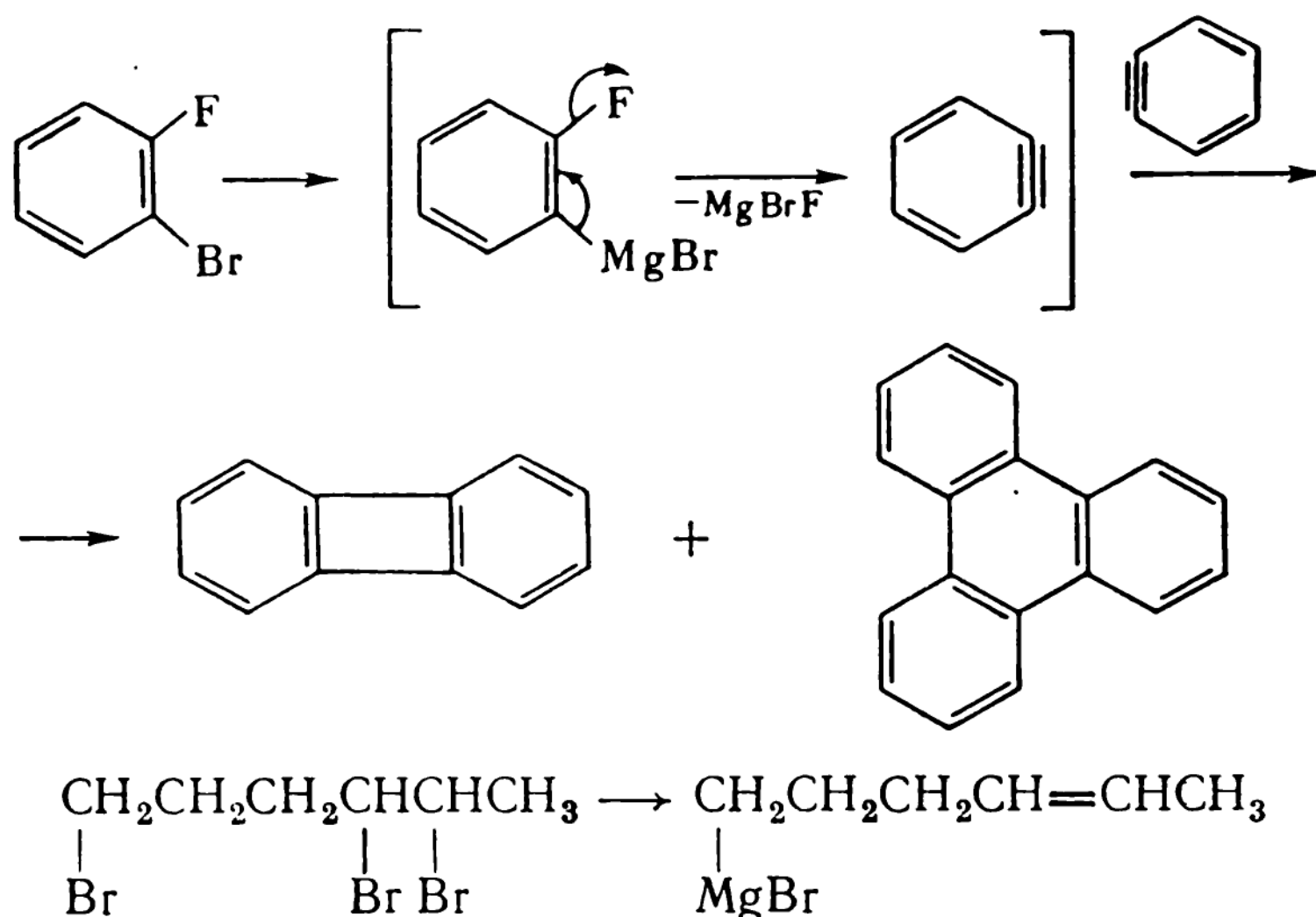
In the *o*-bromobenzylmagnesium bromide obtained the bromine in the benzene ring does not react with magnesium;



8.



(see also answer 14)



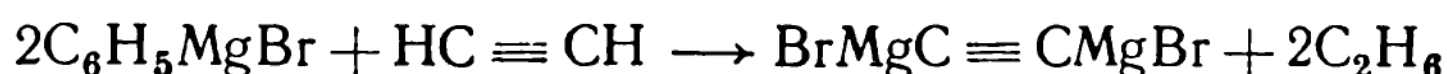
9-10. In solving these problems it should be kept in mind that organomagnesium compounds can be made from almost any alkyl halide (except fluorides) and that the rate of reaction of an alkyl halide with magnesium in ether decreases from iodide to chloride. The yields of organomagnesium compounds decrease in going from primary to tertiary radicals and from chlorides to iodides. The principal side reactions that complicate the preparation of organomagnesium compounds from alkyl halides are dehydrohalogenation and radical coupling reaction similar to the Wurtz reaction. The first process is most characteristic of branched alkyl halides, especially of iodides (*tert*-butyl iodide, for example, when treated with magnesium in ether gives predominantly isobutylene); the second process proceeds the easier the more mobile (see Chapter 3, Sec. 2) is the halogen in an alkyl halide (for all allyl halides, for example, the coupling of radicals under the influence of magnesium in ether is the principal route of the reaction; see answer 14) and the larger is the radical. On the other hand, under the conditions of organomagnesium synthesis bromobenzene may give the by-product of the Wurtz reaction—diphenyl. Aryl chlorides do not react with magnesium in ether.

12. Phenylmagnesium chloride and also vinylmagnesium bromide (the Normant reagent) can be made by reaction of

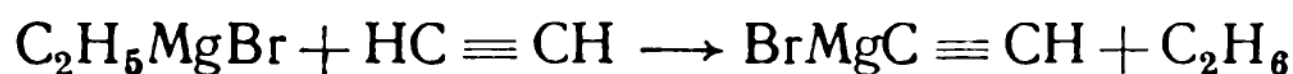
the corresponding halogen derivatives with magnesium in tetrahydrofuran.

Allylmagnesium chloride is made by introducing into the reaction a dilute ethereal solution of allyl chloride with a large excess of magnesium. This reduces to a minimum the possibility of interaction of the unreacted allyl chloride with the allylmagnesium chloride formed, i.e., the side reaction leading to the coupling of allyl radicals and to the formation of diallyl (hexa-1,5-diene) is suppressed.

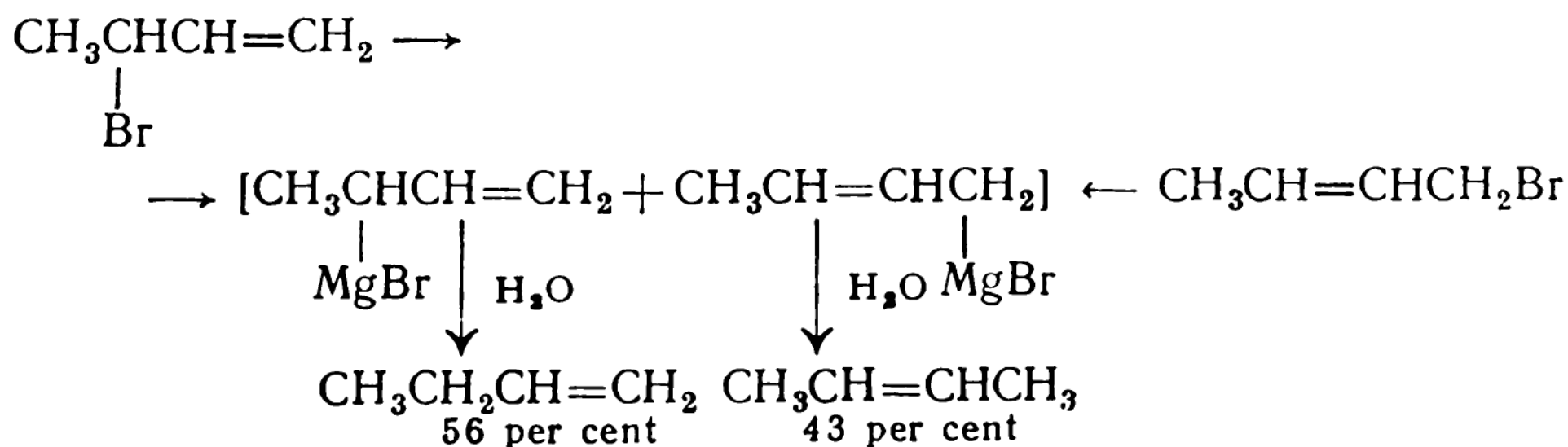
Dibromodimagnesium acetylene (the Iotsich reagent, sometimes called the Iotsich complex) is made by passing acetylene into ethylmagnesium bromide or any other available alkylmagnesium halide



Monobromomagnesium acetylene can be synthesized by adding a solution of ethylmagnesium bromide in tetrahydrofuran to a saturated solution of acetylene in the same solvent



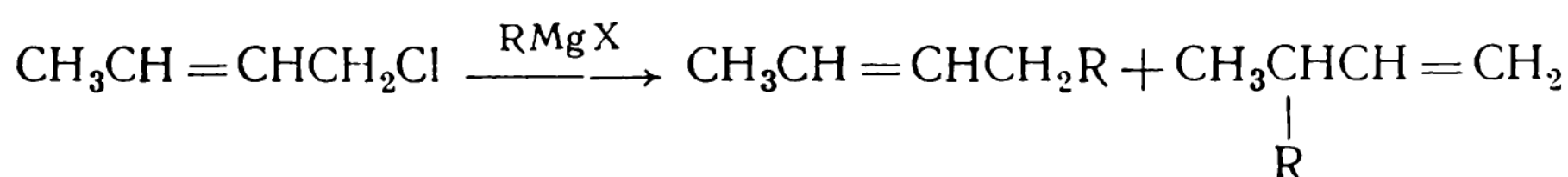
14. In preparing organomagnesium compounds from allyl halides there often occur rearrangements, as a result of which the same mixture can be obtained from each isomeric halide. For example, the treatment of 3-bromobut-1-ene and 1-bromobut-2-ene with magnesium in ether and then with water leads to an identical mixture of butenes (56 per cent of but-1-ene and 43 per cent of but-2-ene). This is evidence that each of the bromides gives the same mixture of organomagnesium compounds (the preparation of organomagnesium compounds from allyl halides is described in answer 12)



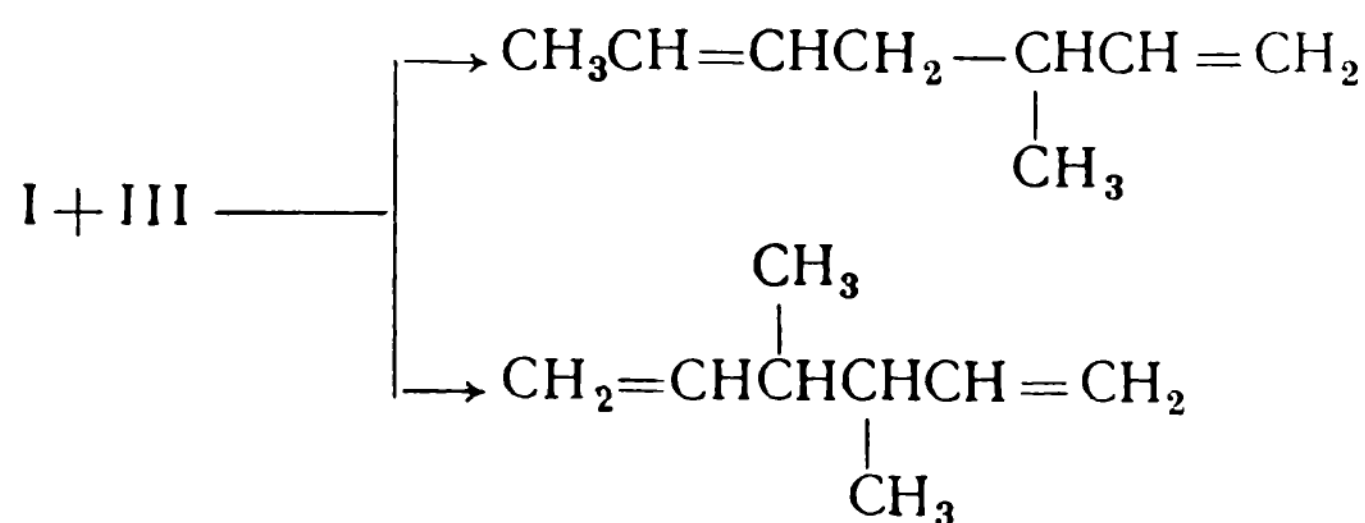
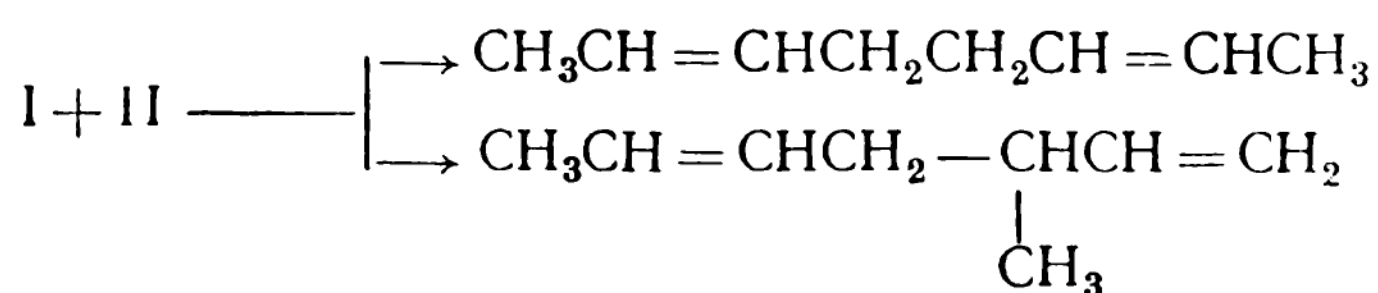
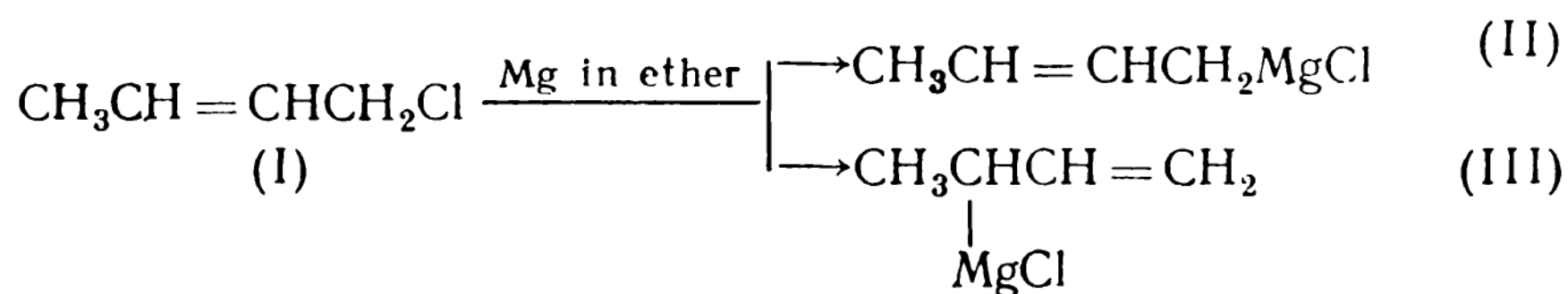
Thus, from crotyl chloride (1-chlorobut-2-ene), if special precaution measures are taken (see answer 12), there can be

obtained, just as in the case described above for crotyl bromide (1-bromobut-2-ene), a mixture of two organomagnesium compounds.

To predict what products will result from the interaction of crotyl chloride with magnesium in ether under ordinary conditions one should take into account that the reaction of halides of the allyl type with organomagnesium compounds also involves a rearrangement. For example,



Hence, crotyl chloride first forms two organomagnesium compounds and then, like allyl chloride, gives with each of them two products

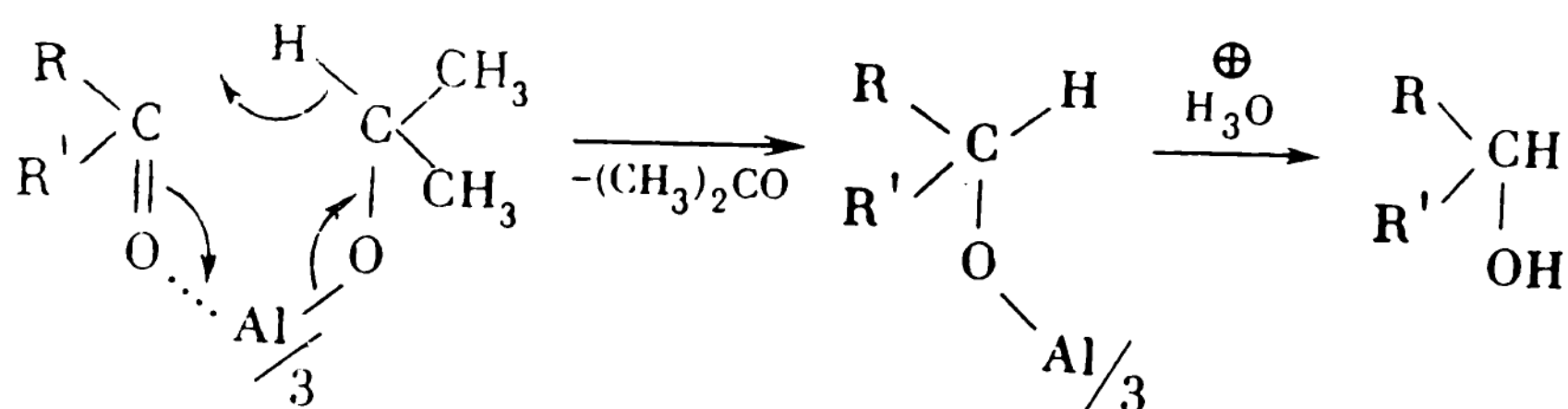


Thus, a mixture of three diene hydrocarbons may result from the reaction of crotyl chloride with magnesium in ether under ordinary conditions.

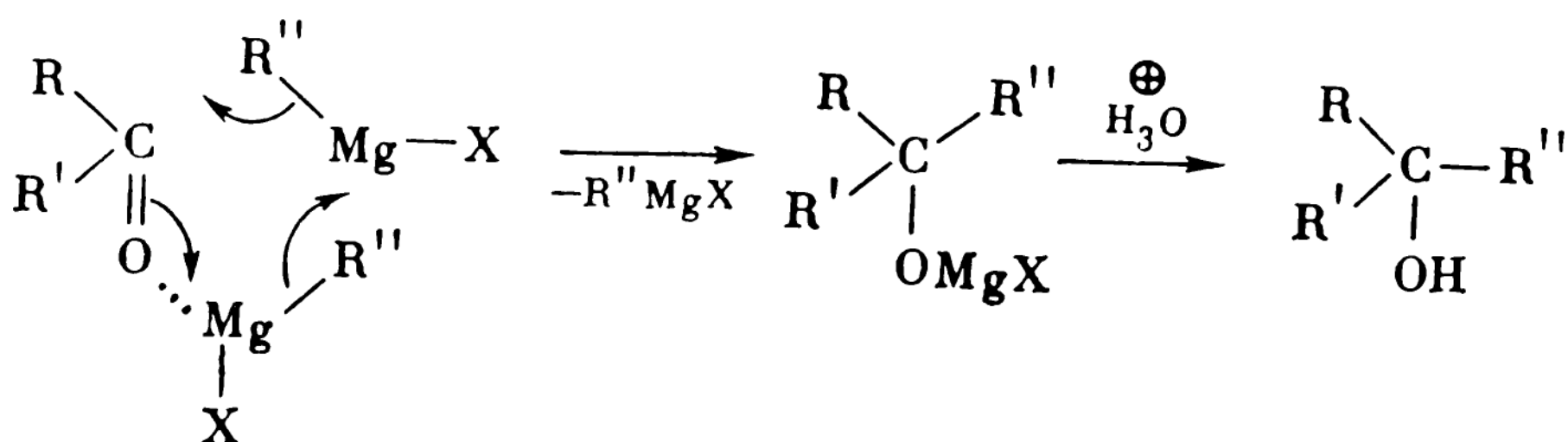
18. The reduction of aldehydes and ketones to alcohols may proceed not only as a result of the free-radical addition of hydrogen to the carbonyl group. This process very often involves two stages proceeding in just the same manner as

the reduction of ketones by aluminium alkoxides (see Chapter 5): first the hydride ion adds on to the carbonyl group carbon and then the alkoxy ion (or the alkoxide) is converted to an alcohol by adding a proton (the alkoxide is hydrolysed). The addition of Grignard reagents at the carbonyl group is a process analogous to the above-described second route of reduction; the only difference is that at the first stage of the reaction not the hydride ion but the carbanion adds on to the carbonyl group carbon (R^- in the equation given below).

The reduction by aluminium alkoxides:



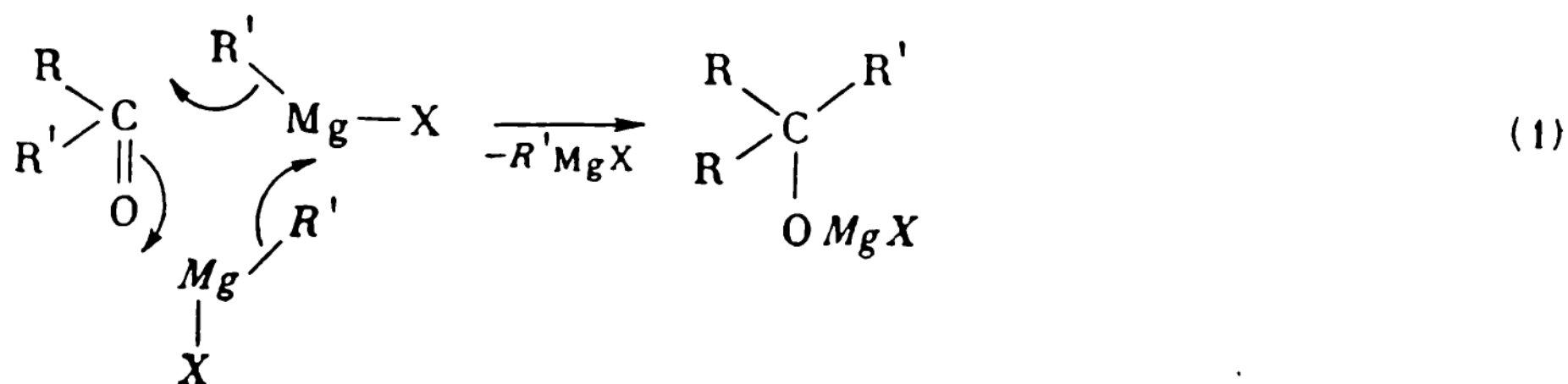
The addition of a Grignard reagent at the carbonyl group:



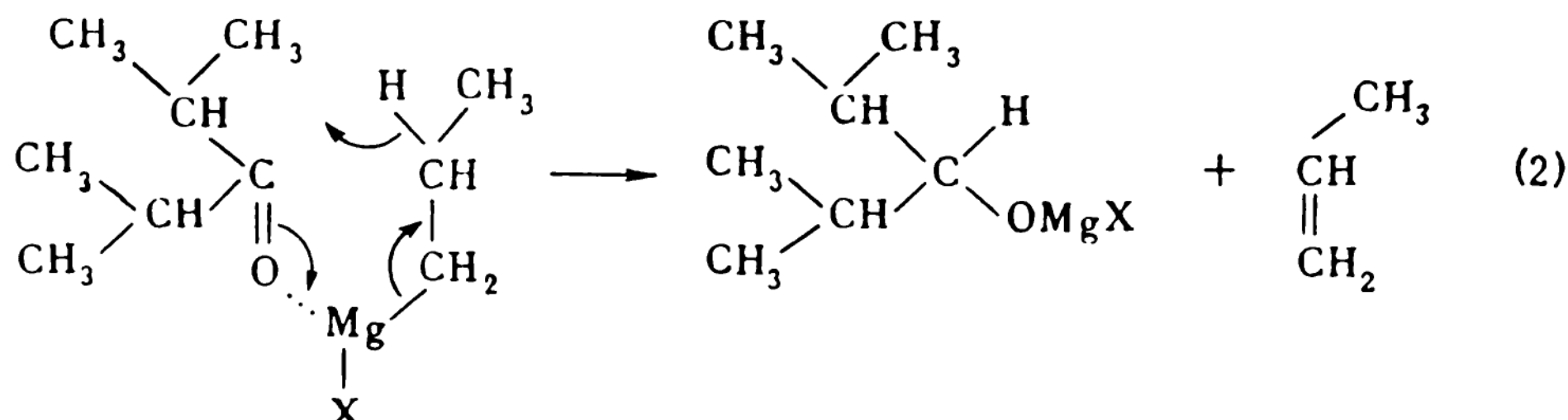
In both cases the reduction occurred at the stage of addition of a negatively charged nucleophilic particle to the carbonyl carbon atom.

19-21. Ordinarily the addition of a Grignard reagent to carbonyl compounds gives almost quantitative yields. A complex is formed in the course of the reaction which involves a carbonyl compound and two molecules of a Grignard reagent; one of them (printed in *italics* in the formula given below) acts as a Lewis acid (see Introduction to the present section and also Problem 58) and increases the electrophilic activity of the carbonyl group and simultaneously enhances

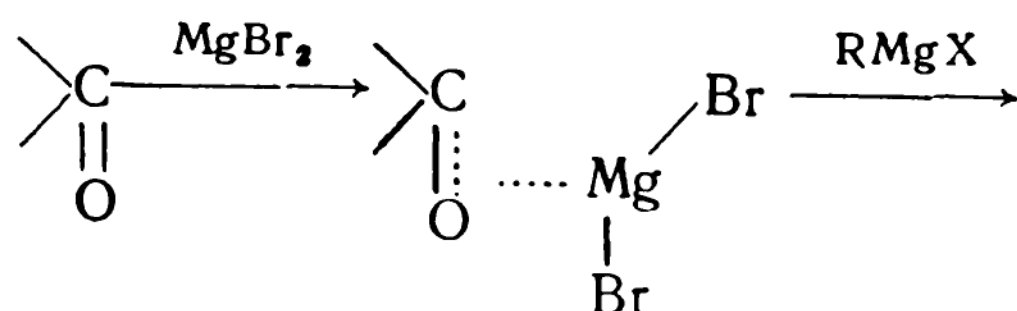
the nucleophilic strength of the second molecule which is a carbanion donor:

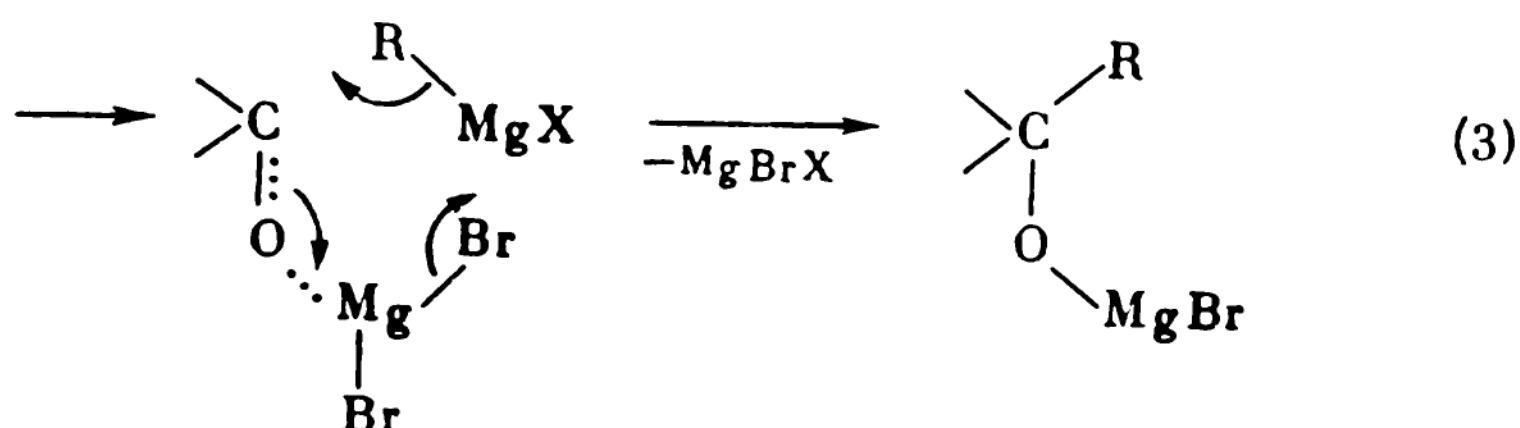


When a carbonyl compound or a Grignard reagent has bulky substituents, there is space in the cyclic complex only for one molecule of the organomagnesium compound. In such cases not the carbanion (R^-) but the hydride ion, which is less bulky, goes over to the carbon of the carbonyl group. As a result, the carbonyl compound is reduced with its carbon skeleton not being complicated and the organomagnesium compound is converted into an olefin:

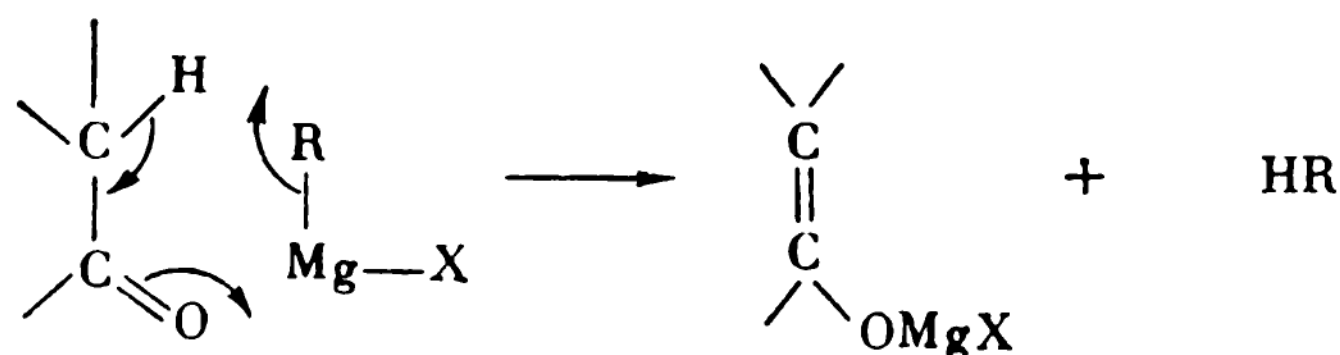


But if a complex of a ketone with magnesium bromide is made before a sterically hindered ketone or Grignard reagent having a bulky radical is introduced into the reaction, magnesium bromide, while increasing the electrophilic activity of the carbonyl group of the ketone, will not (because of its small volume) hamper the incorporation of a molecule of the Grignard reagent into the cyclic transient complex. In this case the reduction of ketone, which proceeds as a side reaction without its carbon skeleton being complicated, will be considerably suppressed:



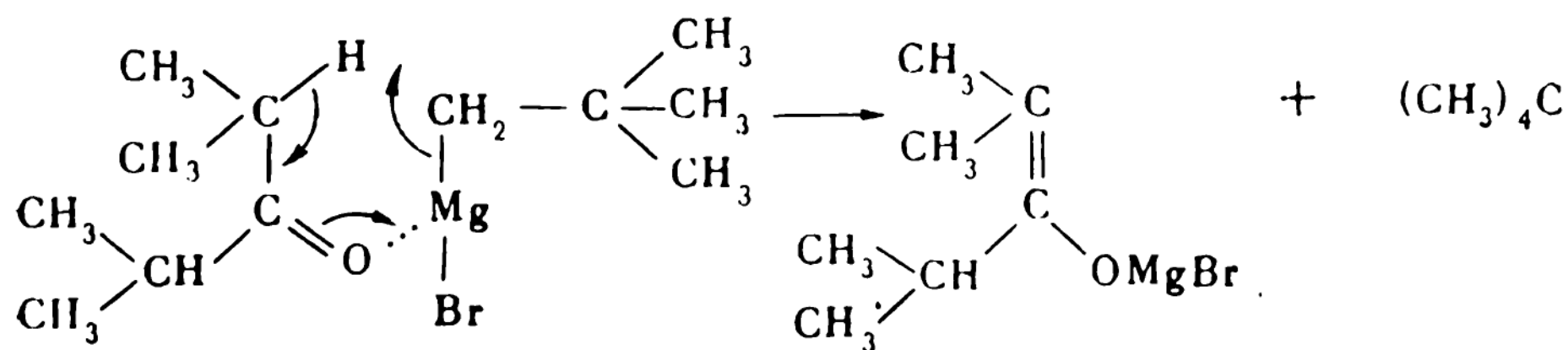


If the molecule of an organomagnesium compound contains a bulky radical, which has no hydrogen atoms in the β -position, the reduction according to the above scheme (see equation 2) is then impossible, and the addition by the usual route proceeds slowly (especially when the ketone is sterically hindered). In this case the principal route of the reaction is the enolization of the ketone (here the inorganic part of the Grignard reagent exhibits the properties of a Lewis acid and the radical, those of a Lewis base)



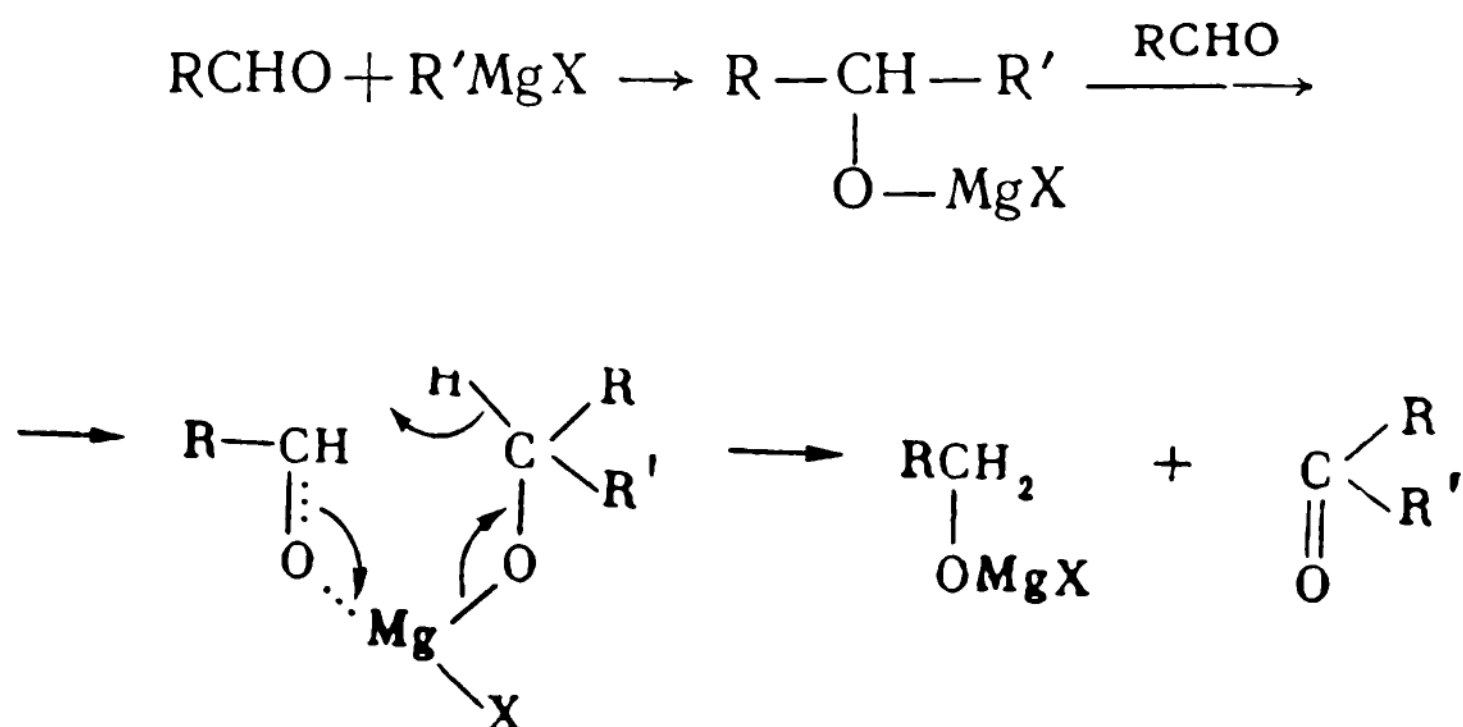
If the reaction takes such a course, the hydrolysis of the reaction mixture gives the original ketone.

It should be kept in mind that occasionally a new series of side reactions result from the enolization; the ketone enolate formed condenses with a second molecule of the ketone, which is in the ordinary non-enolized state, by the aldol or croton mechanism (see Chapter 4). Enolization may naturally take place only when the ketone contains at least one hydrogen atom at α -carbon atoms. An example of the enolizing effect of a Grignard reagent is the reaction of neopentylmagnesium bromide (which contains no hydrogen atoms in the β -position) with diisopropyl ketone (a sterically hindered ketone), which gives a 90 per cent yield:



The above considerations show that the multiple-stage synthesis of tertiary alcohols should be planned in such a way as to introduce the smallest alkyl group at the last stage.

22. *Magnesium alkoxides* formed in the preparation of alcohols by the Grignard reaction are capable of reducing the starting carbonyl compound, just like aluminium alkoxides (see answer 18). The reducing agents causing this side reaction may naturally be only the alkoxides of primary and secondary alcohols (the alkoxides of tertiary alcohols contain no hydrogen atoms capable of splitting off as hydride anions). Hence, such a side reduction process may be observed only when aldehydes are involved:

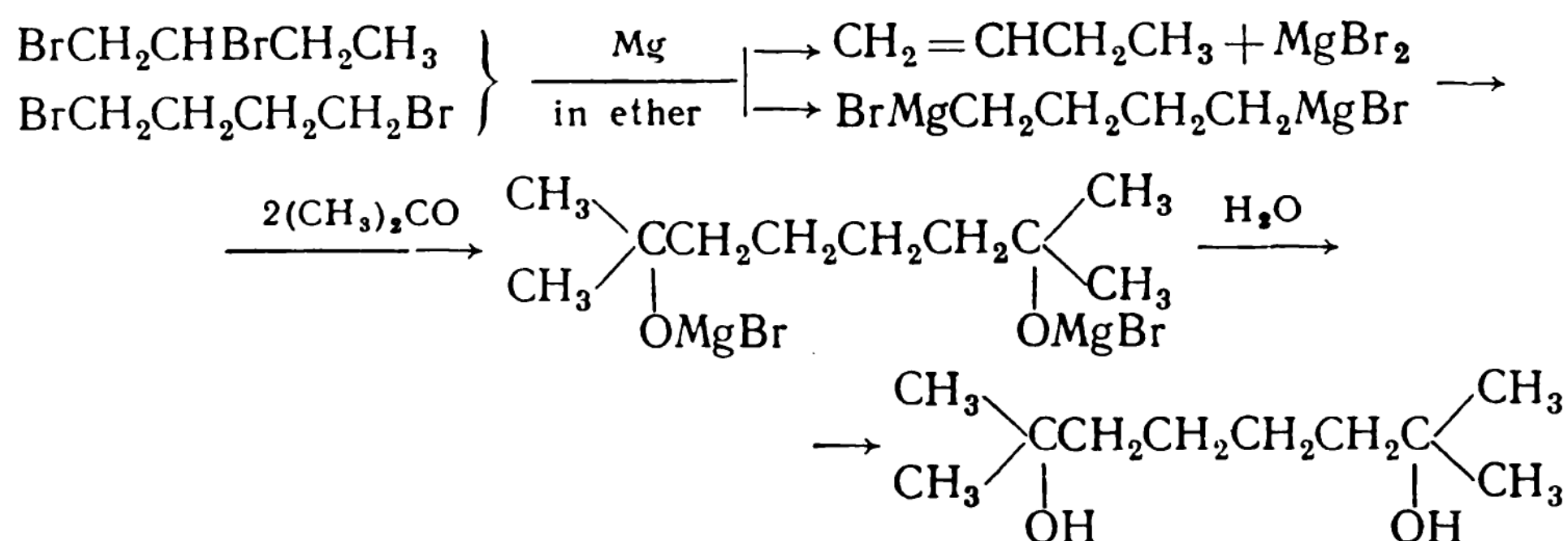


As seen from the equation given above, for the reaction to proceed there must be an excess of an aldehyde that oxidizes the alkoxide formed. Naturally, for this reaction to be suppressed and the normal product of the addition of the Grignard reagent to the aldehyde to be obtained there must be an excess of the organomagnesium compound during the entire synthesis. To provide this, the aldehyde is gradually added to the excess of the Grignard reagent during mixing.

23. The yield of diphenylcarbinol when it is prepared from phenylmagnesium bromide and benzaldehyde depends essentially on the order of addition of reagents. To secure the best yield of diphenylcarbinol one should add benzaldehyde to phenylmagnesium bromide. If the reagents are added in the reverse order, there take place the following side reactions (magnesium alkoxide of a secondary alcohol is obtained

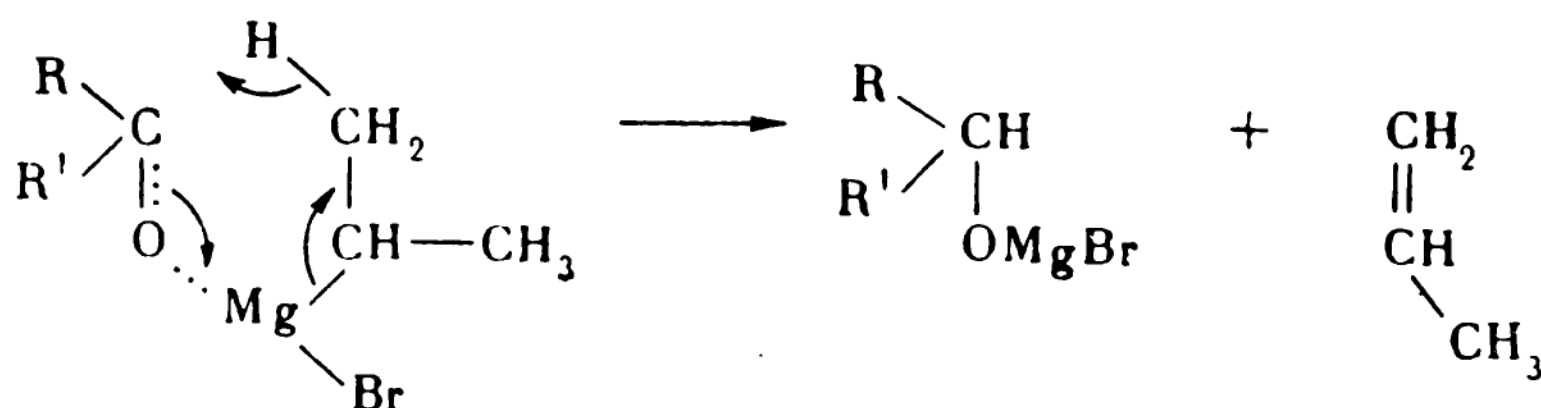
25. In contrast to *tert*-butylmagnesium chloride, neopentylmagnesium chloride has no hydrogen atoms in the β -position relative to magnesium. That is why neopentylmagnesium chloride cannot function as a reducing agent and causes only enolization (see answers 19-21).

28.



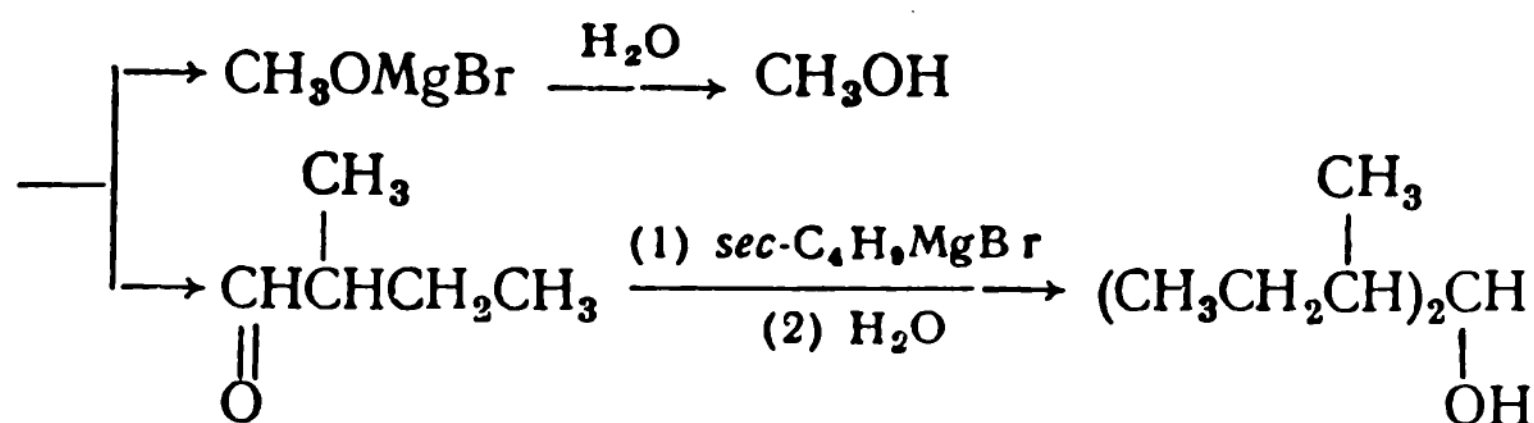
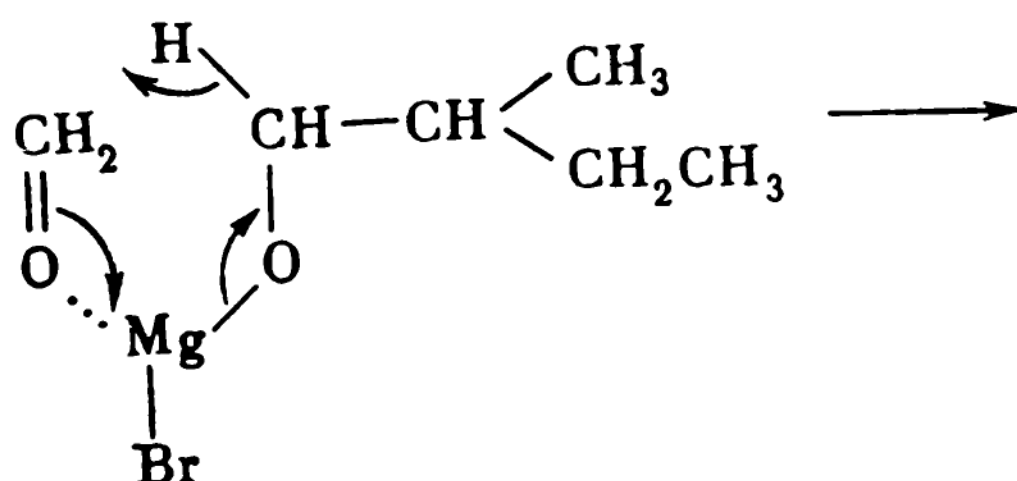
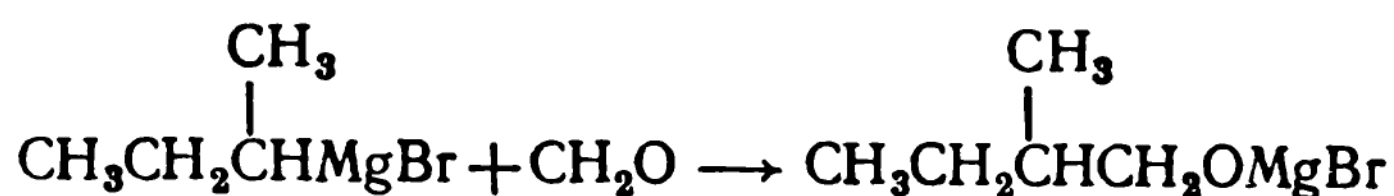
Thus, when a mixture of 1,2- and 1,4-dibromobutanes is treated with magnesium in ether and then with excess acetone and water, but-1-ene and 2,7-dimethyloctane-2,7-diol are formed.

29. Steric hindrances arising in the interaction of isopropylmagnesium bromide with ketones containing bulky radicals are responsible for the fact that only one molecule of the Grignard reagent forms a complex with a ketone molecule (see answers 19-21). In this complex the hydride ion is transferred much more rapidly than the isopropyl anion. The reaction results in the formation of propylene (the gas is evolved) and a secondary alcohol:



To prevent the reaction from taking such a course magnesium bromide should first be added to a solution of the ketone in ether and the resulting complex should be added to the organomagnesium compound (see answers 19-21).

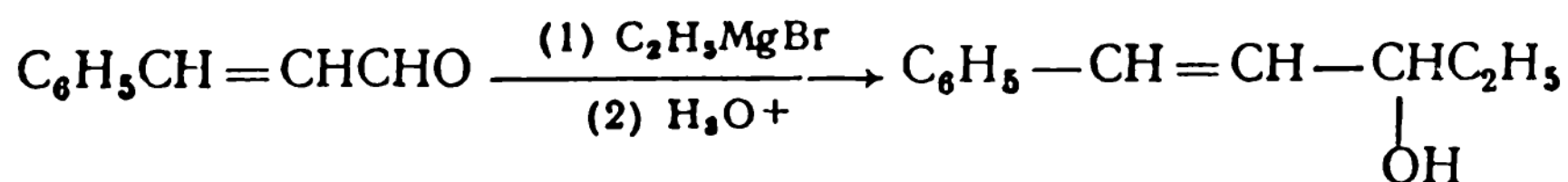
31.



To avoid the occurrence of a side reaction an excess of the organomagnesium compound should be maintained in the reaction mixture (see answers 22 and 23).

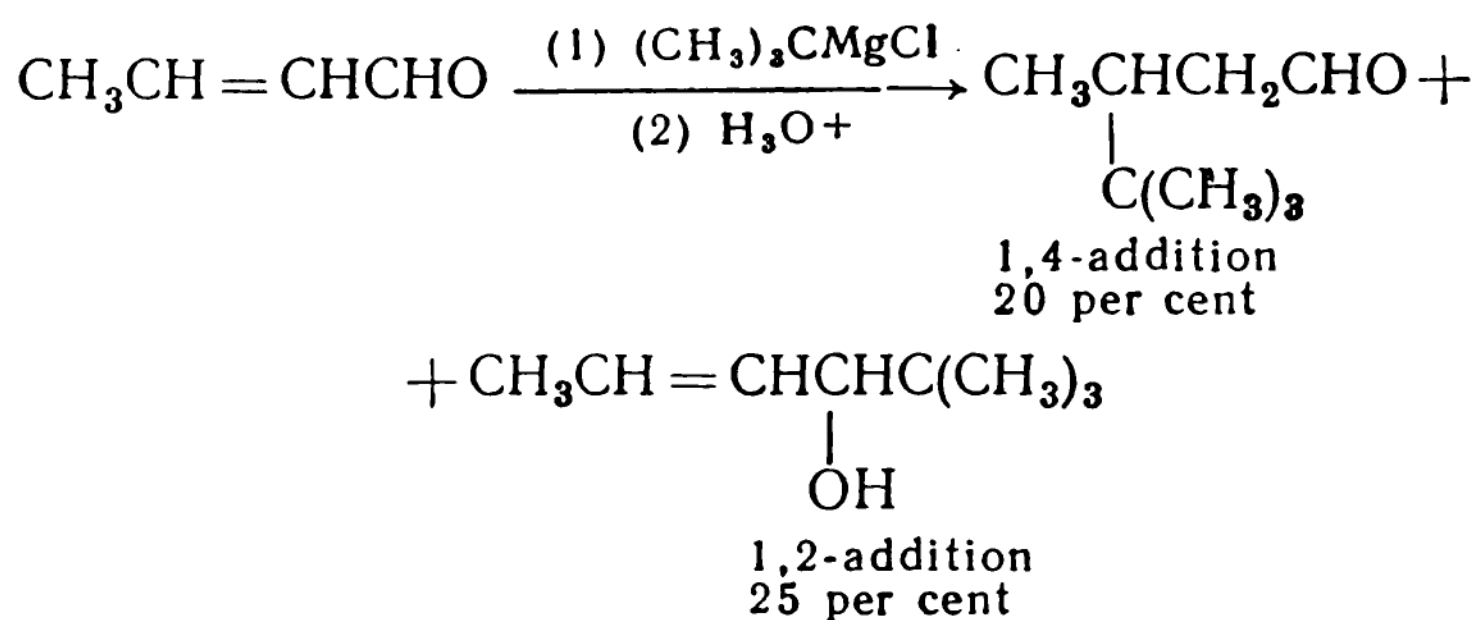
34. α , β -Unsaturated carbonyl compounds contain a conjugated system of multiple bonds $\text{---}\overset{4}{\text{C}}=\overset{3}{\text{C}}\text{---}\overset{2}{\text{C}}=\overset{1}{\text{O}}$. Grignard reagents can add on to this system in the 1,2- and in the 1,4-position.

Aldehydes react, as a rule, across the 1,2-position, for example,

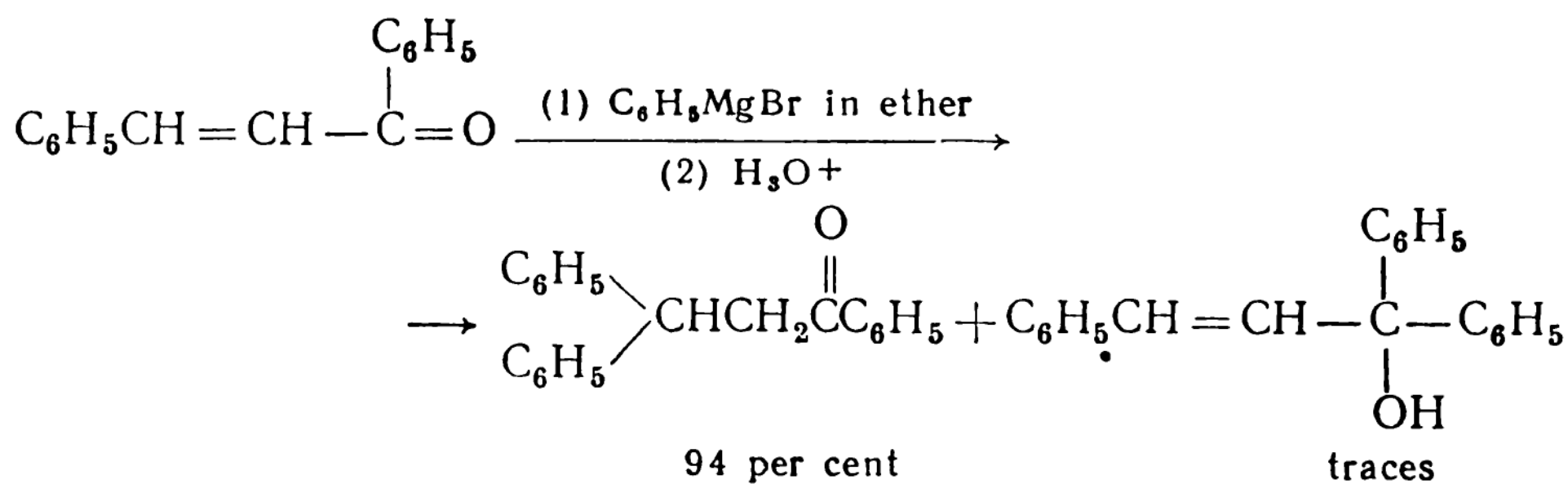


The 1,4-addition takes place only when aldehydes react with Grignard reagents containing a bulky radical, and

to a slight extent at that.

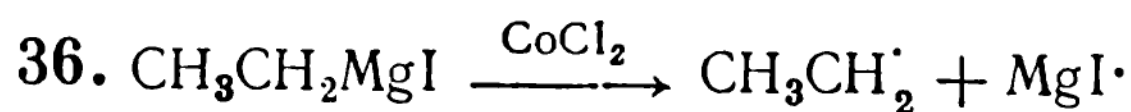


In the case of α , β -unsaturated ketones the addition of an organomagnesium compound across conjugated bonds (i.e., at the 1,4-position) proceeds as a reaction competing with the normal addition across the carbonyl group and is sometimes predominating, for example,

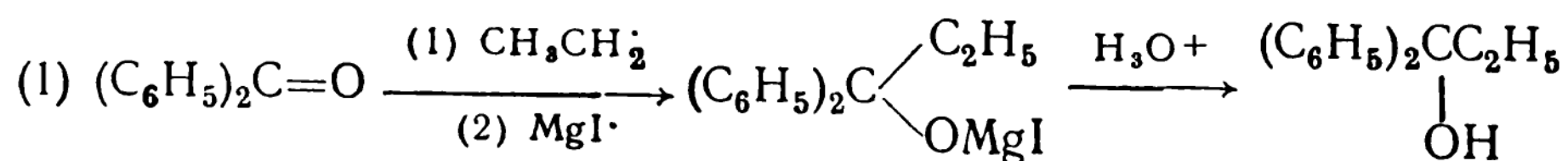


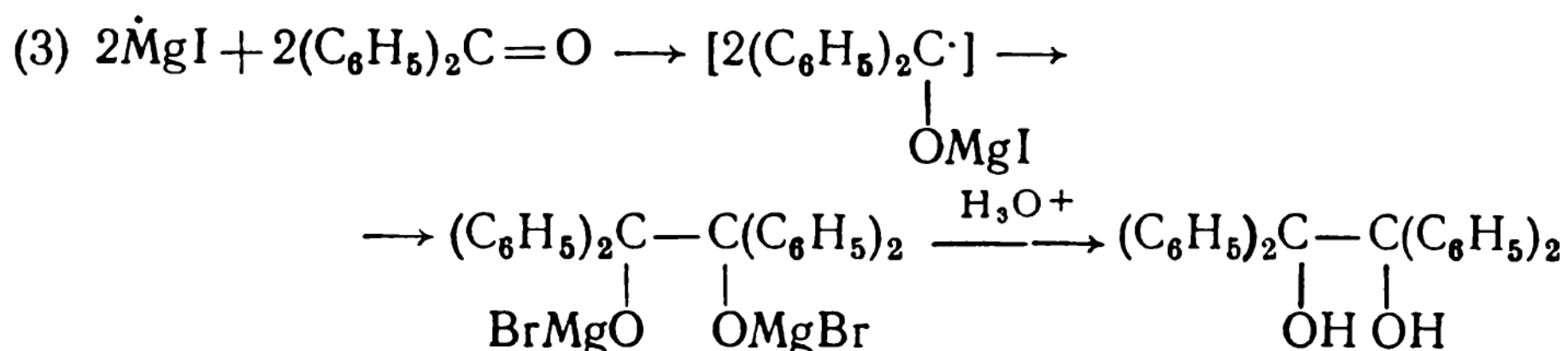
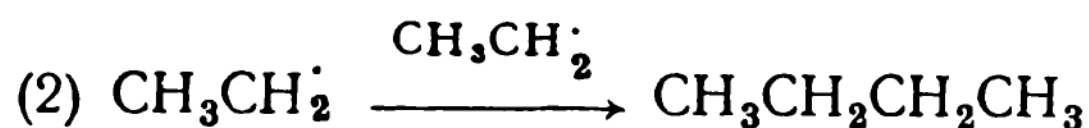
The 1,4-addition proceeds the easier the less is the number of substituents at the carbon atom in the 4-position. In purely aliphatic α , β -unsaturated ketones the predominant route of the reaction is always the formation of a tertiary alcohol (1,2-addition).

35. See the answer to the previous question.



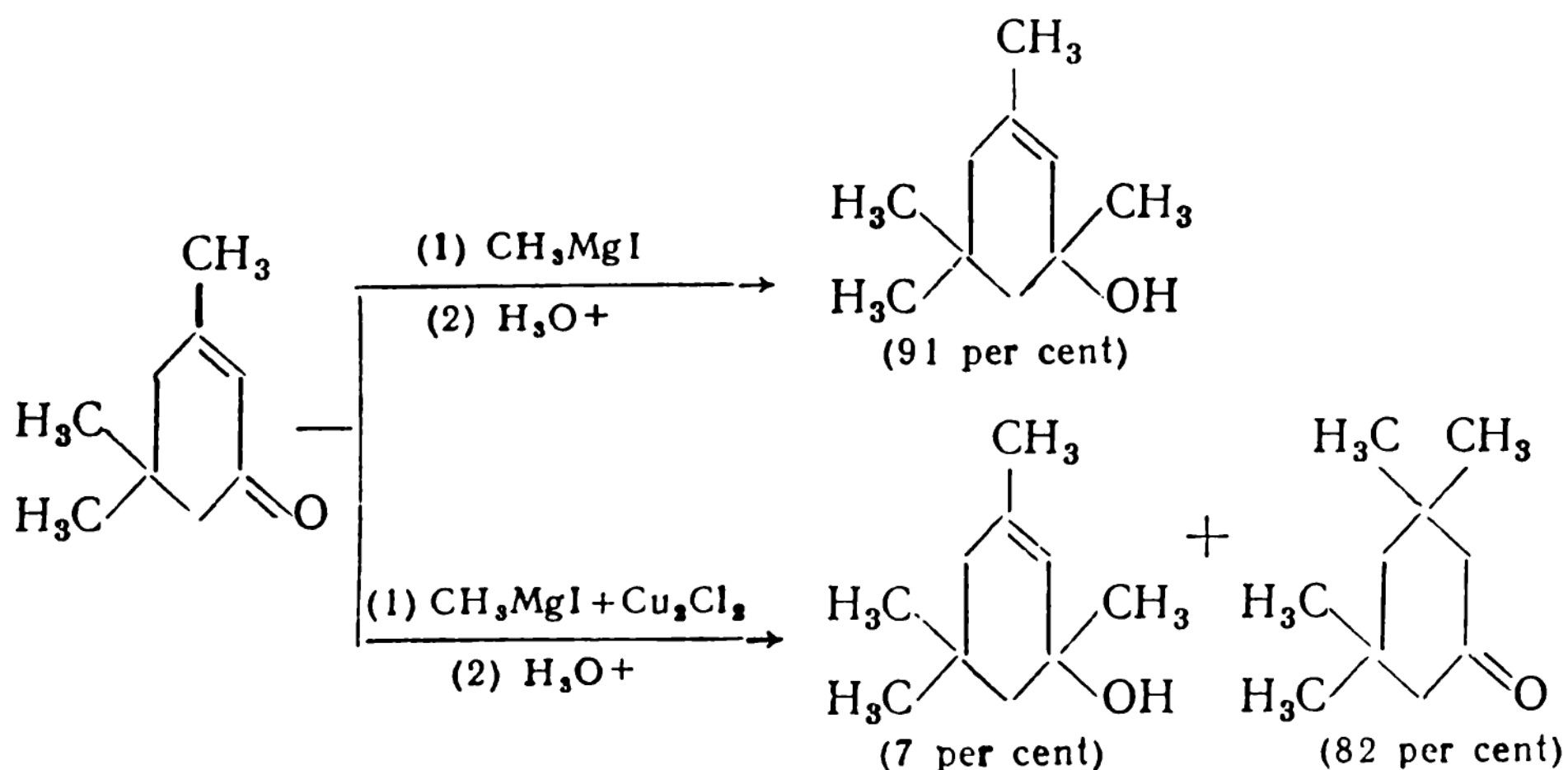
Then the reaction may take one of the following routes:





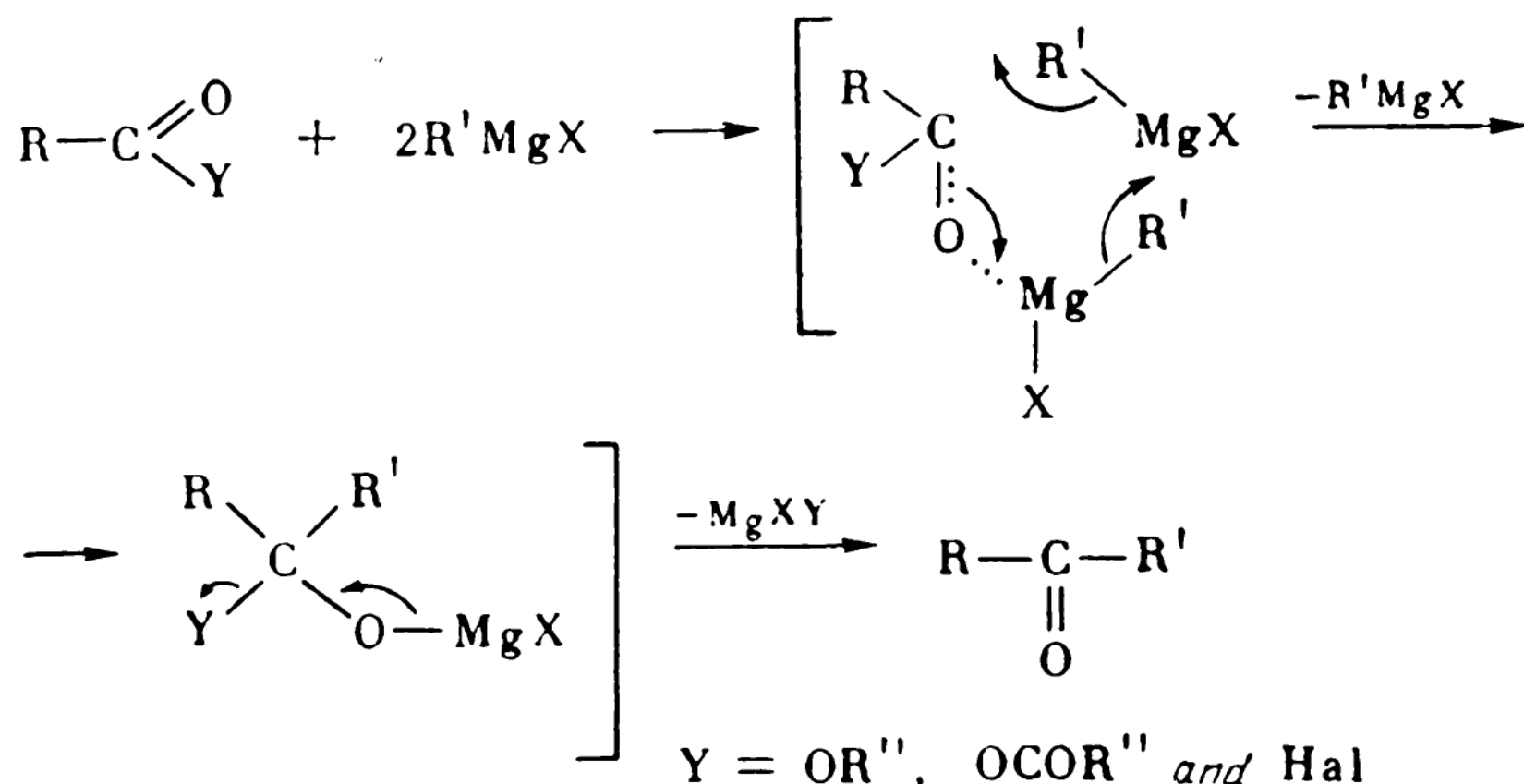
So the interaction of benzophenone with ethylmagnesium iodide in the presence of cobaltous chloride leads to the formation of diphenylethylcarbinol, butane and benzopinacol.

37. Organomagnesium compounds in the presence of cuprous chloride or cobaltous chloride break down into free radicals. This alters the character of their interaction with α , β -unsaturated ketones, which proceeds in this case almost exclusively as a 1,4-addition. An example is the interaction of methylmagnesium iodide with isophorone

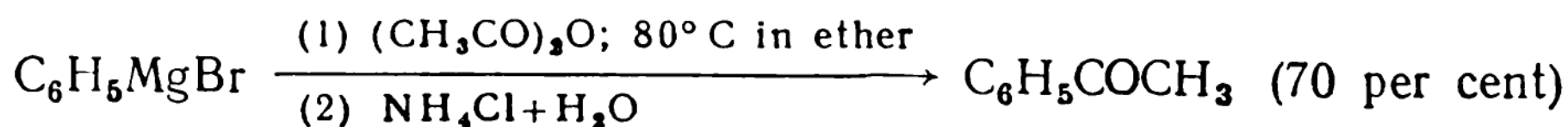


38. The derivatives of carboxylic acids—esters, anhydrides and acid halides—on interaction with Grignard reagents first give adducts, which may be regarded as salts of hemiacetals. Because of the MgX being an electron donor and the group Y an electron acceptor these adducts are unstable

and decompose into a ketone and a molecule of the corresponding alkoxide of magnesium



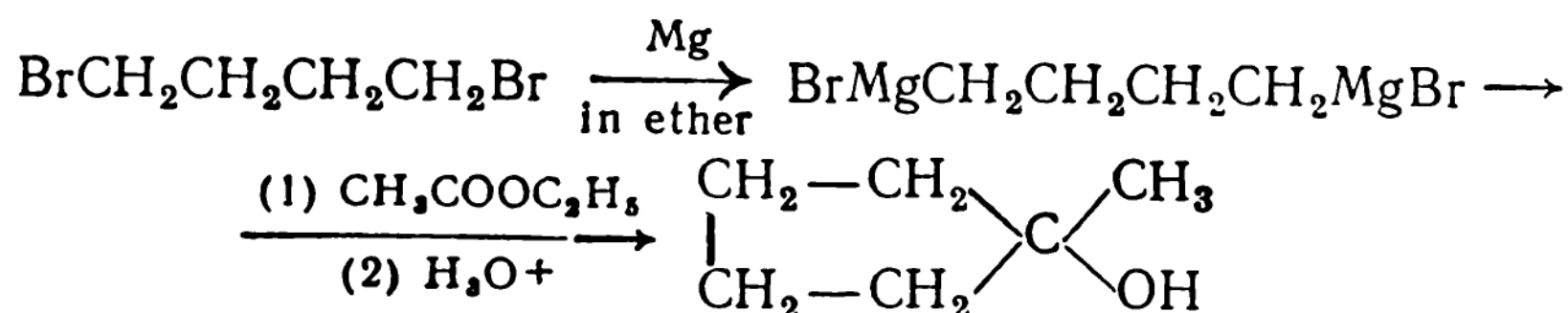
The ketone resulting from this decomposition is superior in reactivity to the starting ester (it has a larger partial positive charge on the carbonyl carbon atom) and inferior to the starting anhydride and acid chloride. Therefore no ketone can be obtained from an ester by organomagnesium synthesis—the ketone formed reacts with the Grignard reagent to give the alkoxide of a tertiary alcohol. But a ketone can be made from an anhydride and an acid chloride provided that no excess of the organomagnesium compound is present in the reaction mixture (i.e., an ethereal solution of the Grignard reagent must be added to the solution of the anhydride or acid chloride in ether) and the reaction is conducted at low temperatures when the difference in the reactivity of the ketone formed and the starting anhydrides is especially pronounced. An example of such a reaction is the synthesis of acetophenone



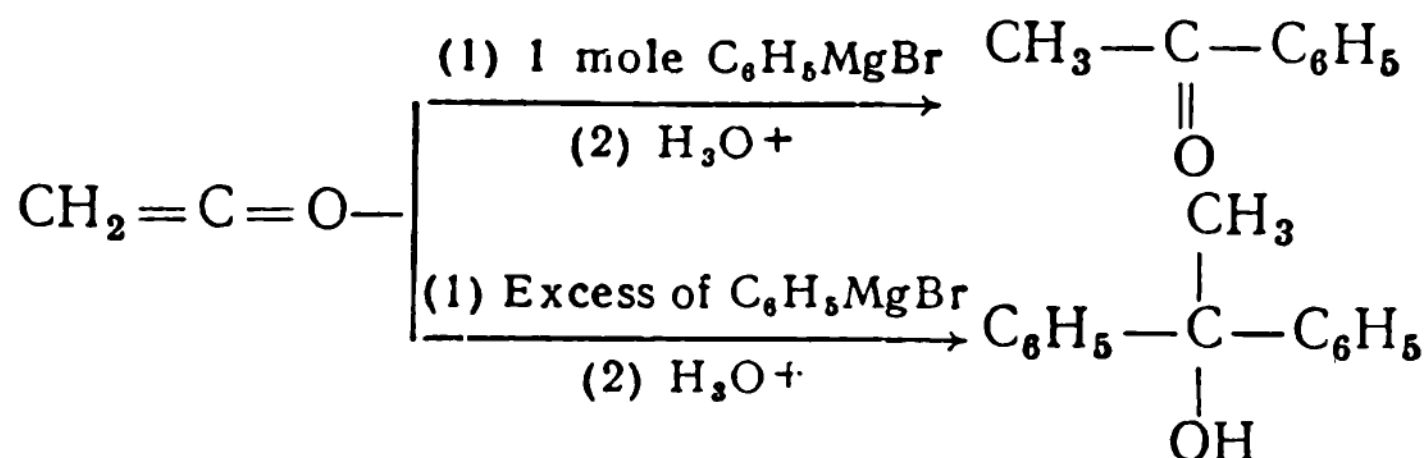
39. See the previous answer.

40. The rate of reaction of Grignard reagents with compounds containing a carbonyl group is governed by the amount of the partial positive charge on the carbonyl carbon atom and also by steric factors (see Chapter 3 for the acylating effect of the derivatives of carboxylic acids and Chapter 4 for the condensation reactions of carbonyl compounds).

41.

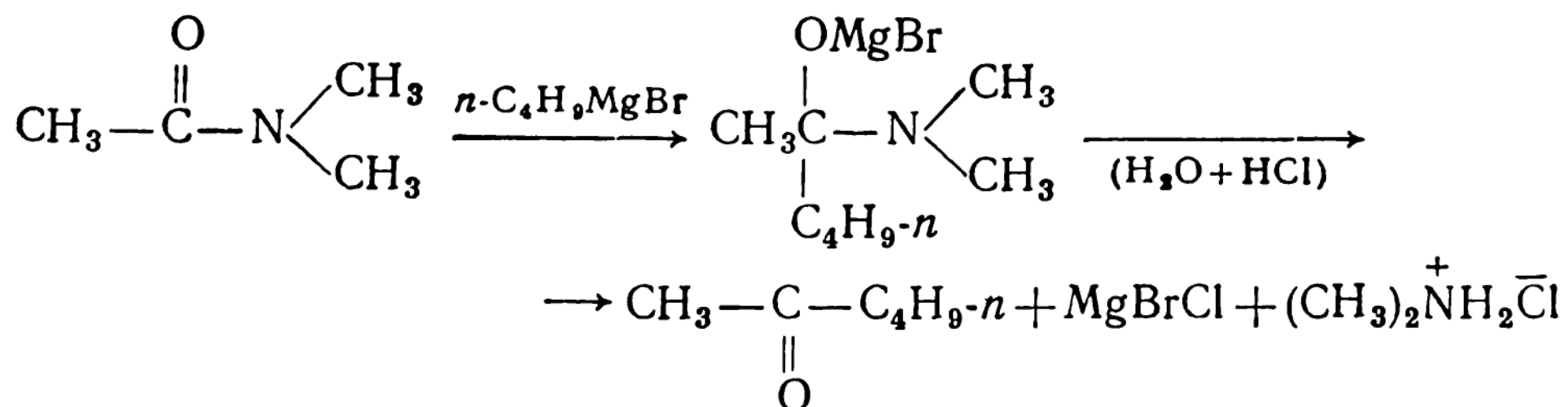


42.

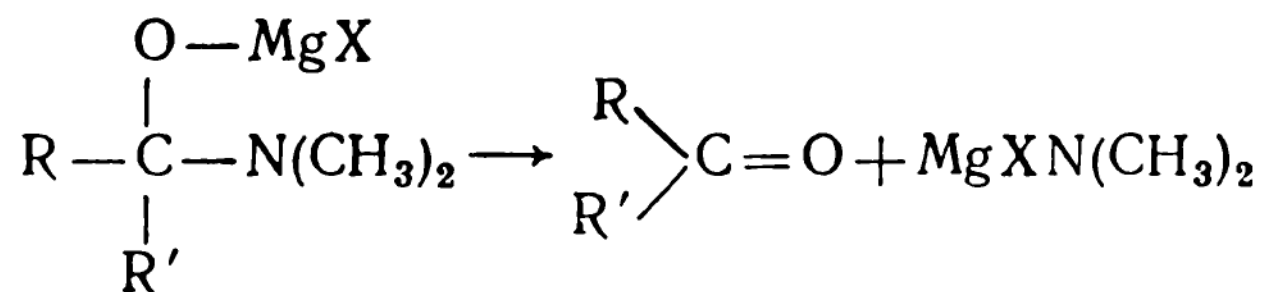


43. See answer 38.

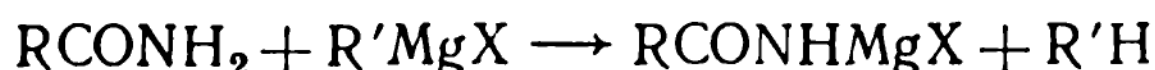
46. N,N-Dialkyl(dimethyl)amides of carboxylic acids often react only with one mole of a Grignard reagent¹. This results in the formation of stable adducts, which on hydrolysis with an aqueous solution of acid give ketones. For example,



In this case the stability of the adducts (as distinct from those obtained from esters, anhydrides and acid chlorides; see answer 38) is due to the low electronegativity of the dimethylamino group and also to the energy unfavourableness of the formation of the corresponding magnesium amide upon decomposition of these products, i.e., to the difficulty of realization of the following process:



¹ Unsubstituted amides react first as compounds with an active hydrogen atom (see Introduction to this section and also Problems 61-68):

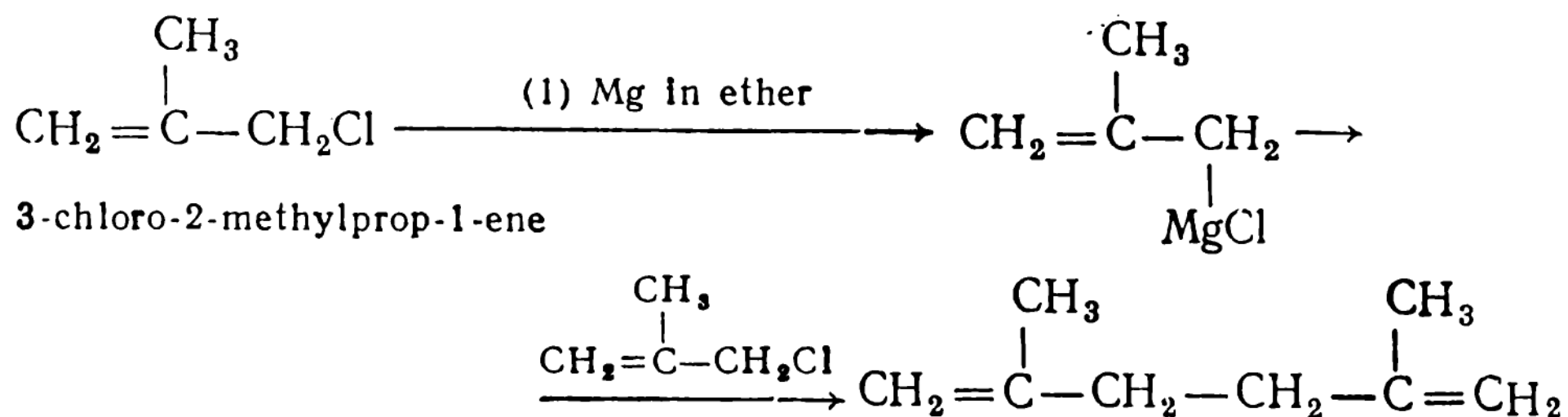


48. Like esters, acid chlorides and anhydrides, the salts of carboxylic acids react readily with Grignard reagents to form the alkoxides of tertiary alcohols (explain why ketones cannot be made from salts of acids whatever the reaction conditions; see answers 38 and 46). Therefore, if it is desirable to obtain a salt of the acid as the product of the reaction (in order to convert it into the acid) the contact of this salt with the organomagnesium compound should be avoided. This condition is best observed if the solution of the organomagnesium compound is poured onto dry ice. It may also be appropriate to introduce quickly pieces of solid carbon dioxide into the flask containing a Grignard reagent. The probability of interaction of the salt formed with the Grignard reagent (and hence the probability of a tertiary alcohol being formed) is the highest if a current of carbonic acid is passed into the solution of the organomagnesium compound. In this case the yield of the corresponding acid is the lowest.

49. In order to obtain vinylacetic acid from allyl chloride it is necessary to prepare from the latter an organomagnesium compound (see answer 12) and then to treat it successively with carbonic acid and dilute mineral acid. Acrylic acid may be made analogously by carbonization of vinylmagnesium bromide (the Normant reagent; for its preparation see answer 12).

50. See answers 9, 10, 12, 14.

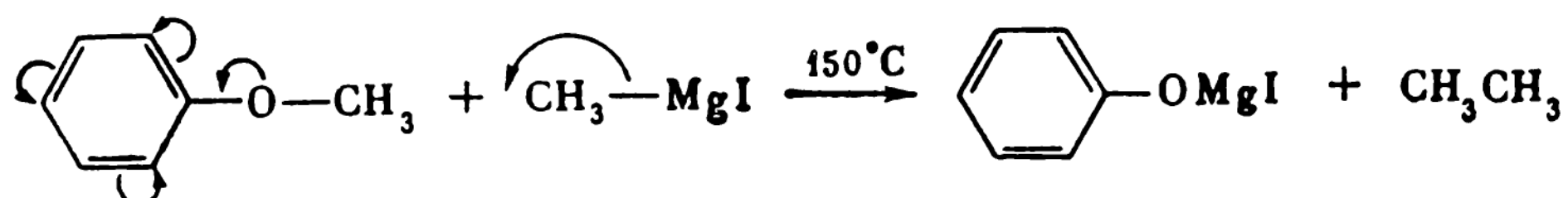
51. Because of the specificity of the structure of allyl chloride, 3-chloro-2-methylprop-1-ene and 4-chloro-2,4-dimethylpent-2-ene the rearrangements (the so-called allyl rearrangements) involved in the preparation of organomagnesium compounds from them and also in their interaction with the Grignard reagent formed will lead exclusively to one reaction product. For example,



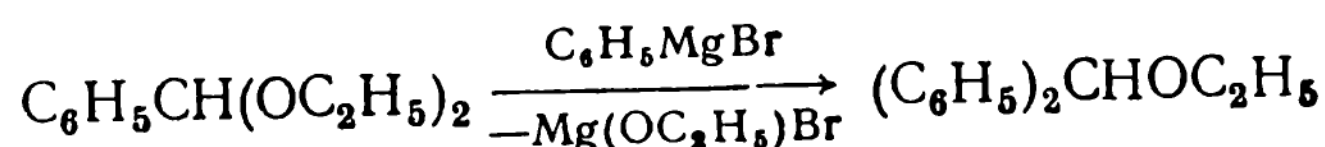
But when magnesium reacts with 2-chlorohex-3-ene in ether, there arises a situation analogous to the one discussed in answer 14.

52. Anisole is a suitable solvent for the preparation of many organomagnesium compounds. However, at temperatures well above 100°C it can be cleaved by Grignard reagents.

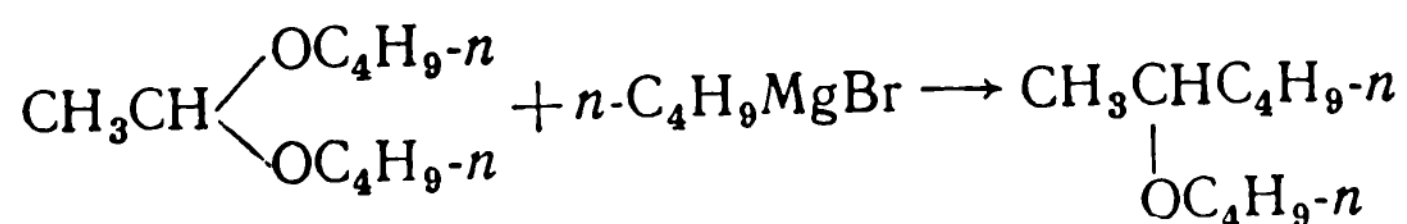
Since the boiling point of anisole is rather high (155°C), its boiling with methylmagnesium iodide is accompanied by the cleavage of the ether bond (in this case the methyl group of methylmagnesium iodide attacks in a nucleophilic way the electron-deficient methyl group of anisole)



53. Acetals and ketals, as a rule, do not react with organomagnesium compounds under ordinary conditions (in an ethereal solution at room temperature). The acetals of benzaldehyde react most easily:

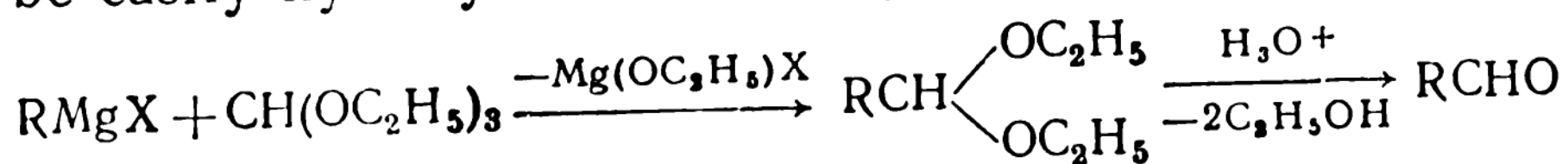


In most cases, for such a reaction to be accomplished, the ether is distilled off after the ethereal solutions of the components are mixed and then the reaction mixture is heated on a boiling water bath:



In the case of ketals the replacement of only one alkoxy group by a radical of an organomagnesium compound may be of preparative value.

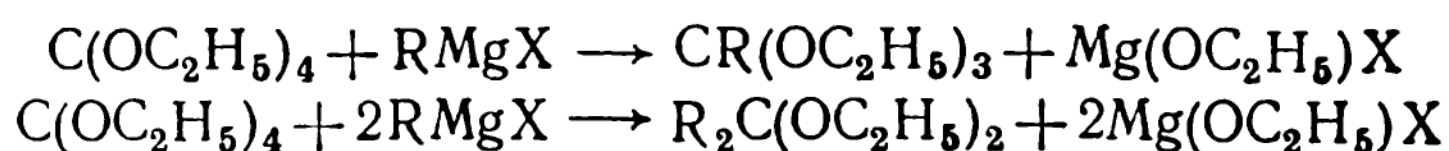
Orthoformic ester reacts under ordinary conditions with organomagnesium compounds to give acetals, which can then be easily hydrolysed into aldehydes:



Under more drastic conditions two alkoxy groups can be displaced by a radical of an organomagnesium compound

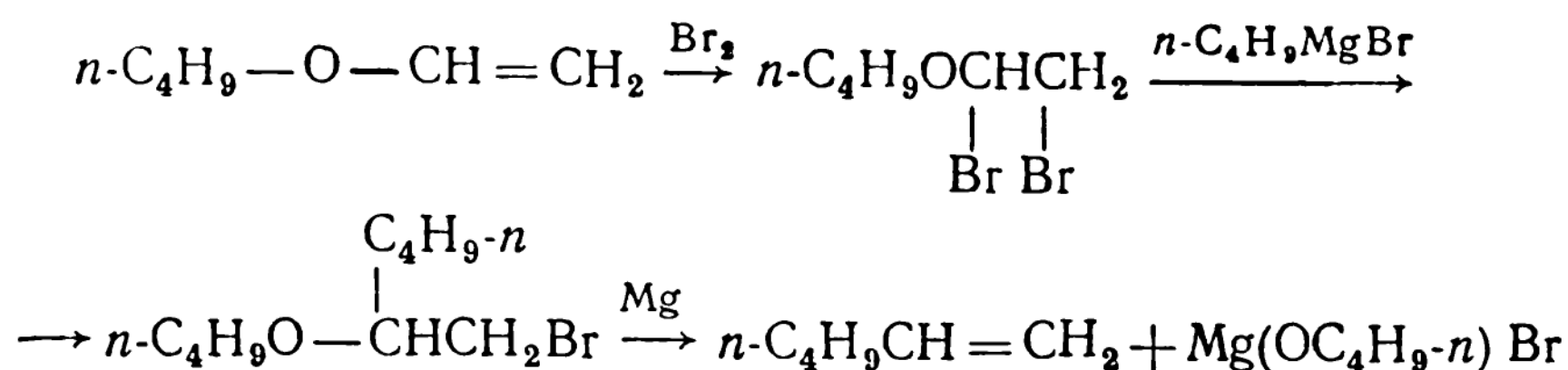
to give ethers of secondary alcohols in low yields (see above). Only the preparation of acetals and of aldehydes from them is of practical importance.

By replacement of the alkoxy groups in orthocarbonate by radicals of an organomagnesium compound there can be obtained orthocarboxylic esters (with an equimolar ratio of the reagents) and ketals (if two moles of the Grignard reagent are taken for one mole of orthocarbonate):

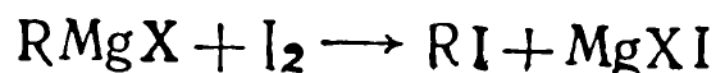


Ketals are hydrolysed to give ketones.

54.



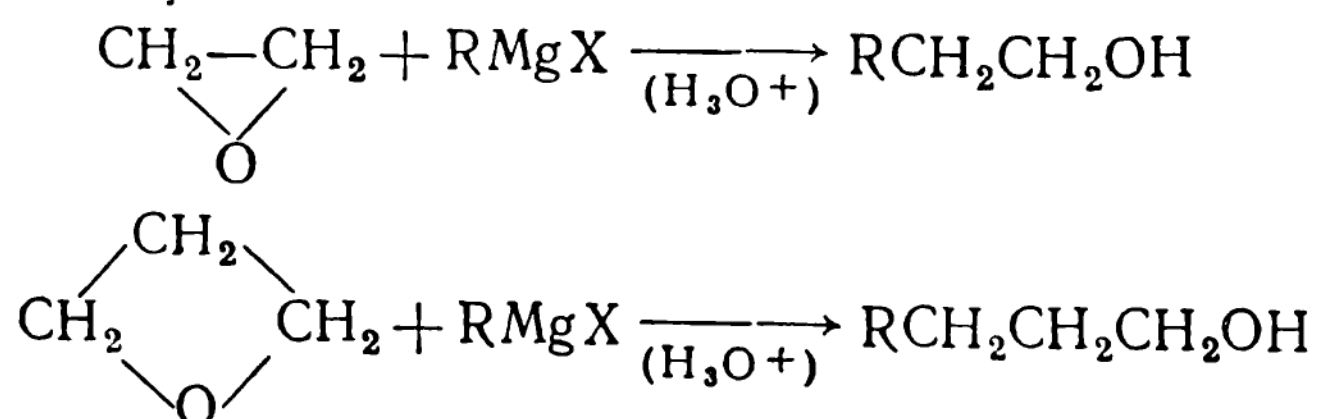
55. An organomagnesium compound is preliminarily treated with an excess amount of iodine. As a result, it is entirely converted into the corresponding iodide:



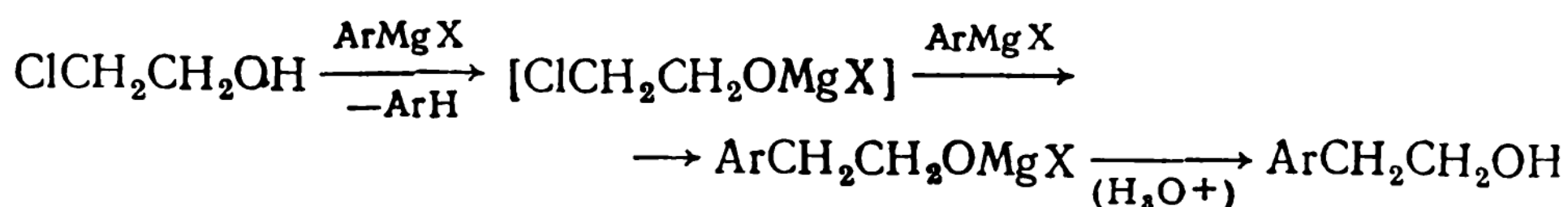
Excess iodine is titrated with thiosulphate. The difference between the amount of iodine introduced into the reaction and the amount of iodine that has not reacted corresponds to the quantity of the organomagnesium compound.

56. See the previous answer.

57. Ethylene oxide and trimethylene oxide, which readily react, with the opening of the oxide ring, with such nucleophilic agents as primary and secondary amines (see Chapter 3), react by the same mechanism with organomagnesium compounds: the hydrolysis of the alkoxides formed results in primary alcohols:

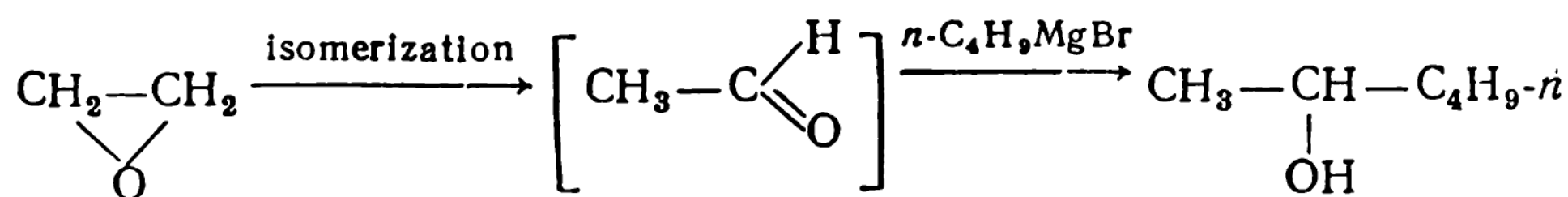


Primary alcohols can also be made from ethylene chlorohydrin without using formaldehyde. The reaction proceeds especially smoothly when arylmagnesium halides are used. For this, two moles of a Grignard reagent for 1 mole of ethylene chlorohydrin are required:



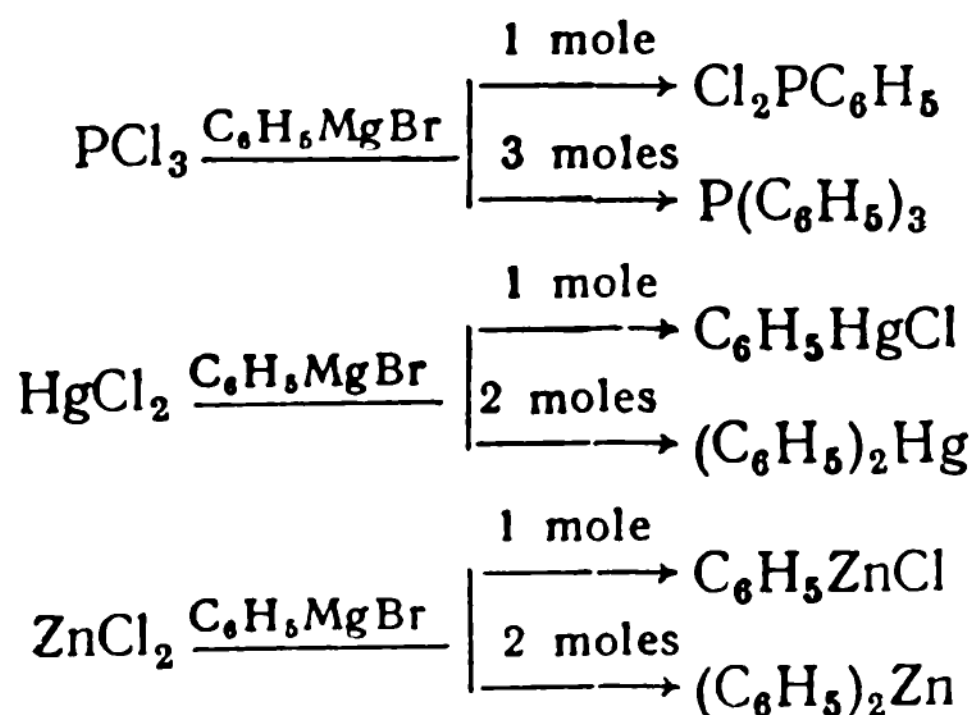
58. As already noted above (see Introduction to this section) Grignard reagents, like magnesium halides, are capable of reacting in the same way as Lewis acids due to the specific properties of the metal. One of these properties—the ability to coordinate with carbonyl compounds—has already been discussed (see answers 19-21 and 29).

The coordination of an organomagnesium compound with ethylene oxide (at the expense of the unshared electron pair on the oxygen atom) may lead to its isomerization if the reaction conditions are not sufficiently mild (dilute solutions, low temperatures). Therefore, the reaction of Grignard reagents with ethylene oxide often leads to the formation of secondary alcohols:



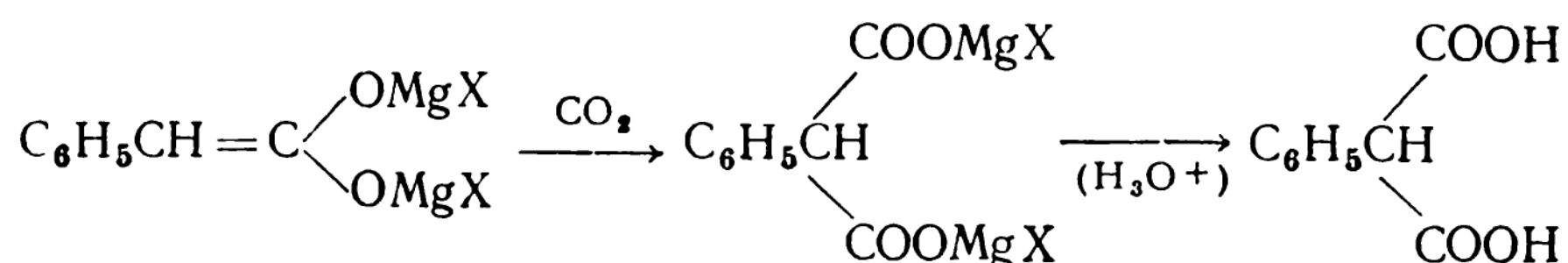
59. There are formed respectively propylbenzene, 1,2,3,5-tetramethylbenzene and *p*-pentyltoluene, i.e., the esters of sulphuric acid react with RMgX as alkylating agents.

60.

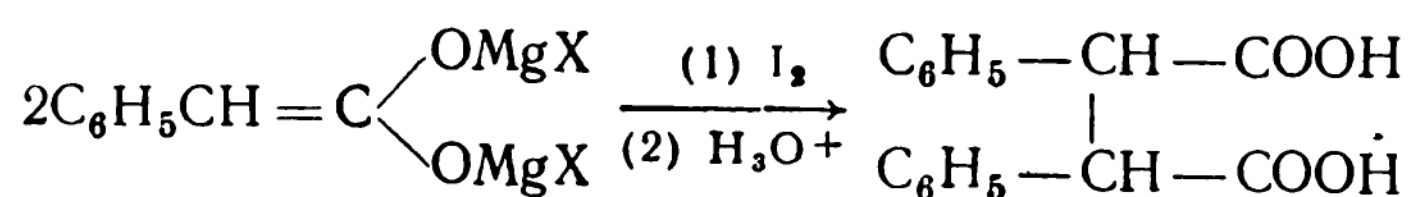


64. The mixture of methyl-*para*-cresol (O^{18}) and iodobenzene should be dissolved in ether and treated with an adequate amount of magnesium. In this reaction iodobenzene will be converted into phenylmagnesium iodide. Phenylmagnesium iodide can be converted into benzene by addition of water to the reaction mixture, the methyl *p*-tolyl ether being unaffected. The resulting mixture of benzene (b.p. 80°C) and methyl-*para*-cresol (b.p. 175°C) can easily be separated into its components by distillation.

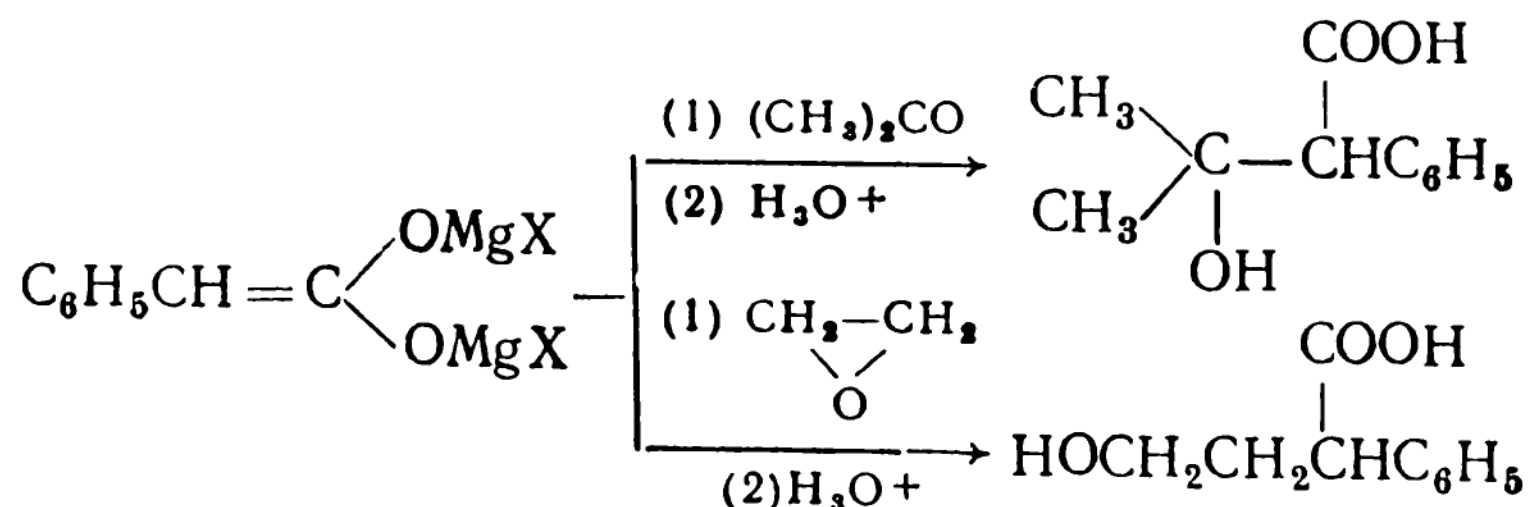
65. Like sodioacetoacetic ester, the Ivanov reagent, $\text{C}_6\text{H}_5\text{CH}=\text{C}\begin{smallmatrix} \diagup \text{OMgX} \\ \diagdown \text{OMgX} \end{smallmatrix}$, reacts with most electrophiles with a carbon atom carrying a partial positive charge not at the oxygen but at the carbon. An example is the reaction with carbon dioxide:



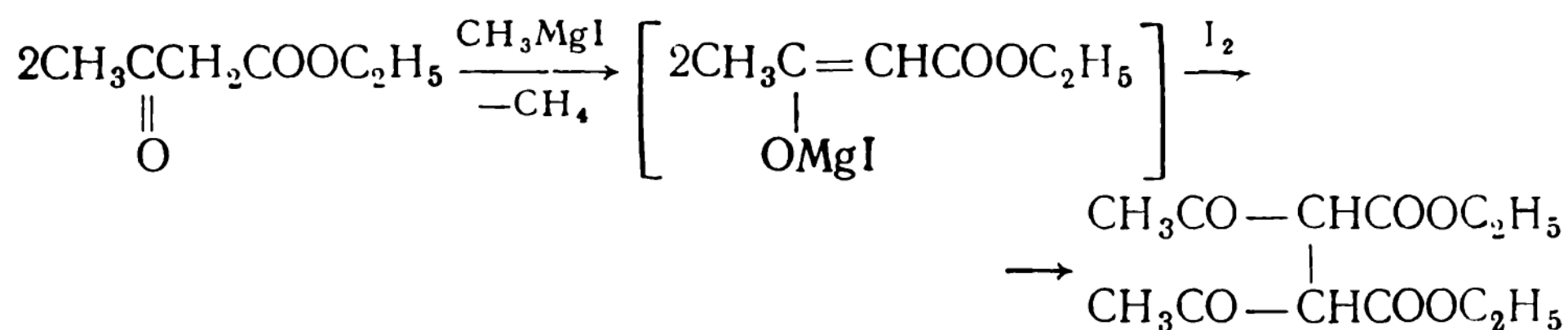
When treated with iodine the Ivanov reagent undergoes coupling (again like sodioacetoacetic ester):



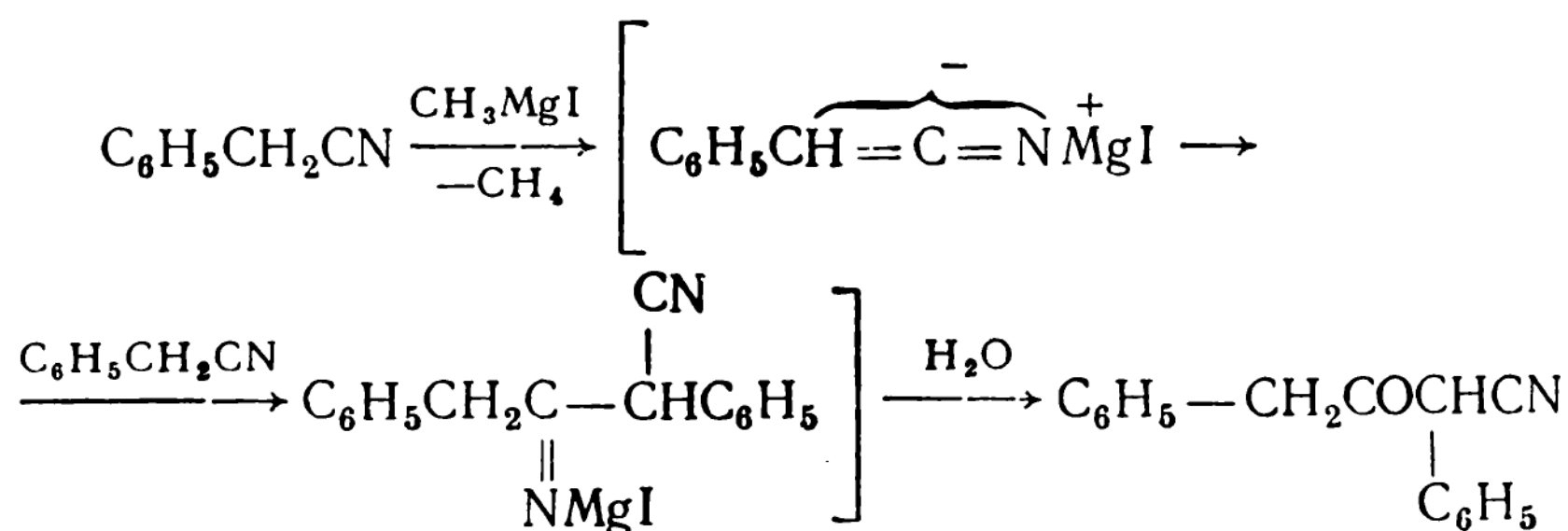
With acetone and ethylene oxide the reaction proceeds in just the same manner as with an ordinary organomagnesium compound



66.



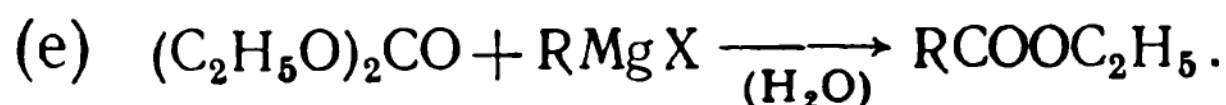
67.



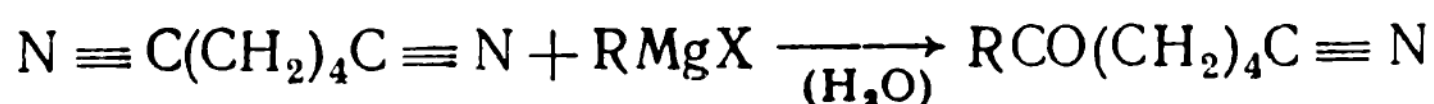
69. (a) 2-Chloropent-3-ene + RMgX → see 14.

(c) Acetoacetic ester + RMgX → see 66; dimethyl sulphate + RMgX → see 59.

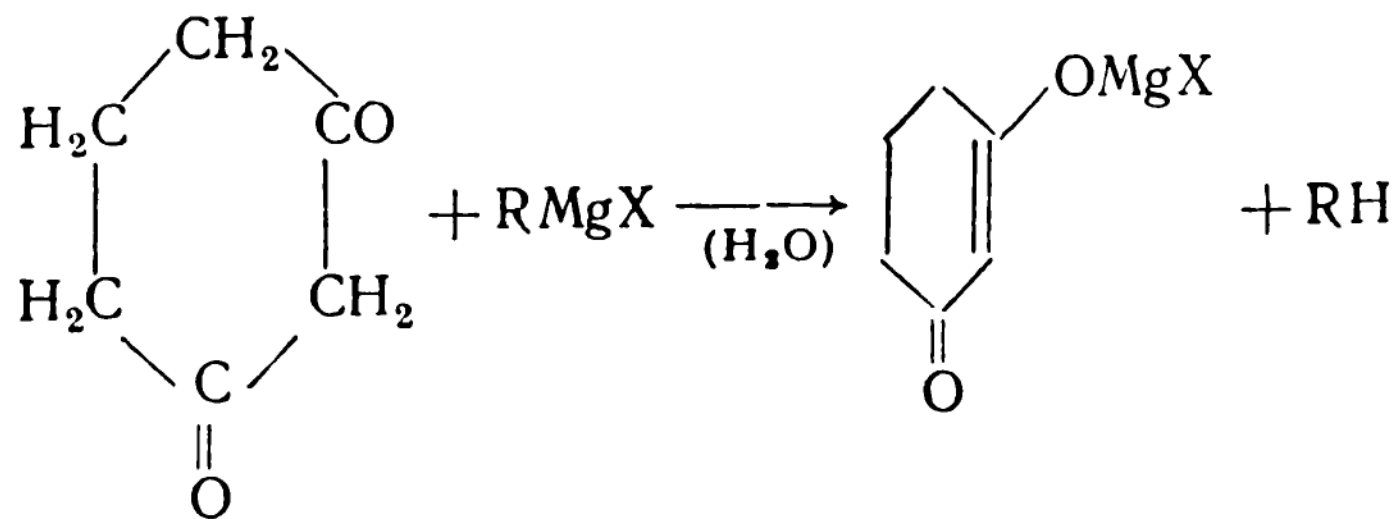
(d) 4-Bromopent-2-ene + RMgX → see 51; diethyl sulphate + RMgX → see 59.



(f) 1-Chlorobut-2-ene + RMgX → see 14,



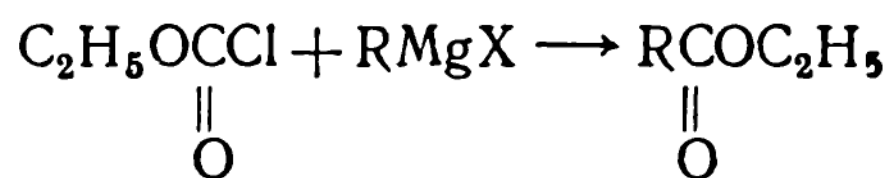
(g)



(see also 54).

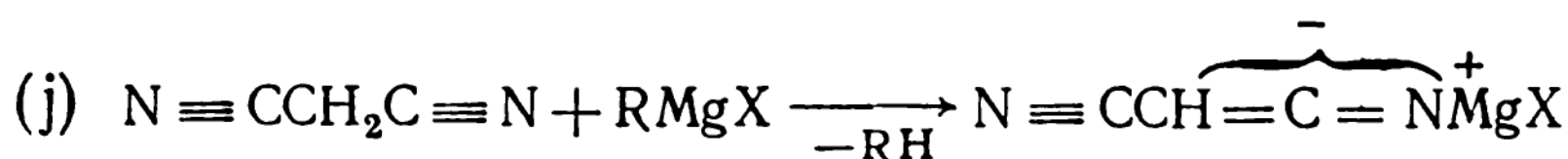
By gradually adding a Grignard reagent to the ester of chlorocarbonic acid (the "reverse" order of addition of rea-

gents) one can obtain an ester of the acid containing one carbon atom more than the starting alkyl halide:



(see also 38).

(i) Phthalic anhydride + RMgX → see 38.



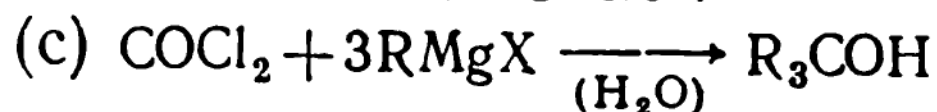
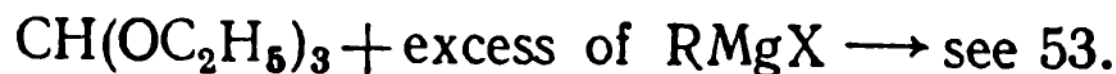
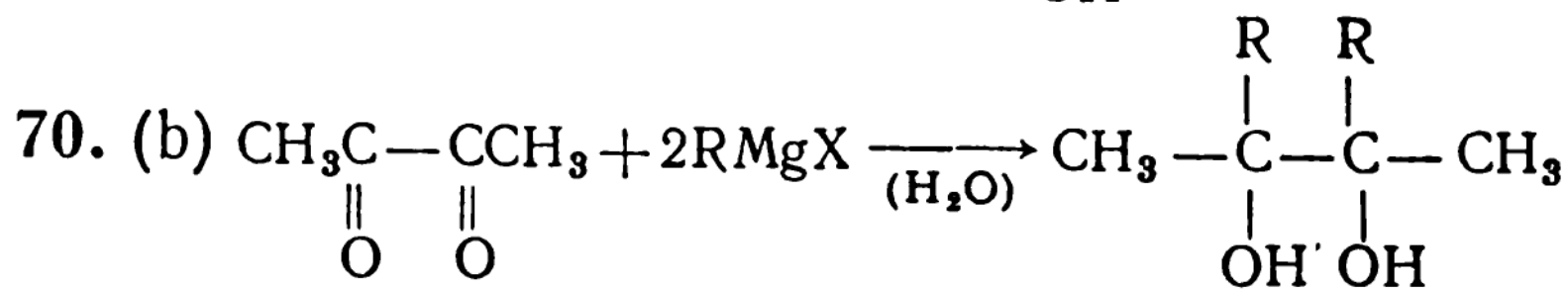
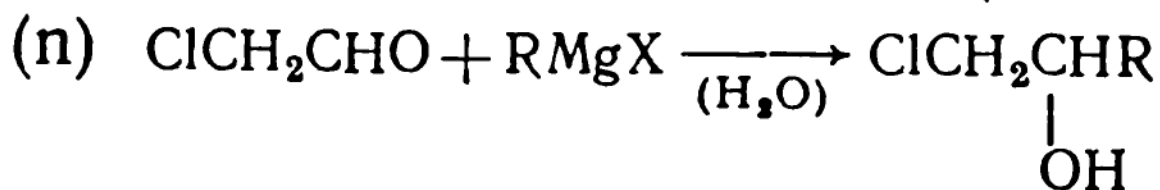
(see also 67).

(k) α,β -Dibromoethyl-*n*-butyl ether + RMgX → see 54.

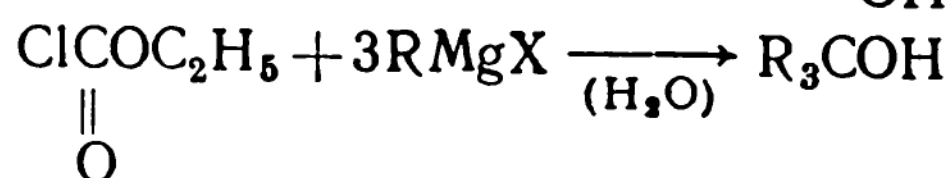
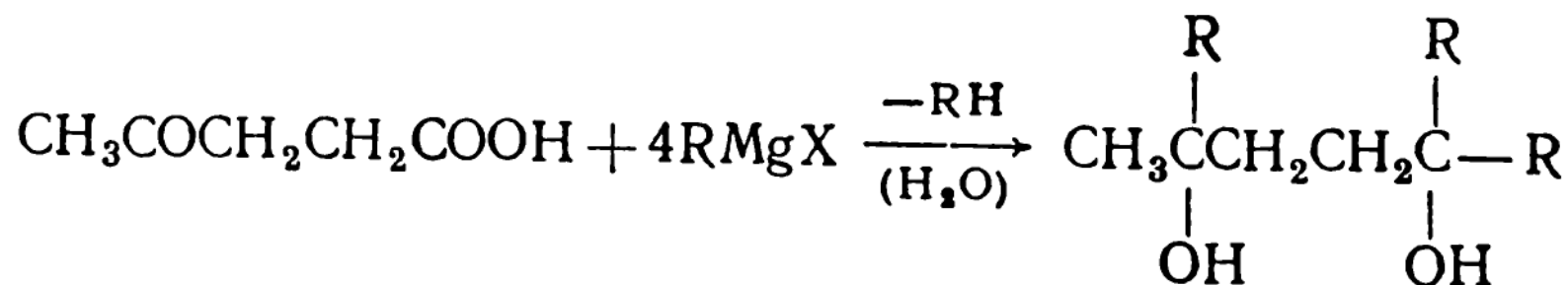
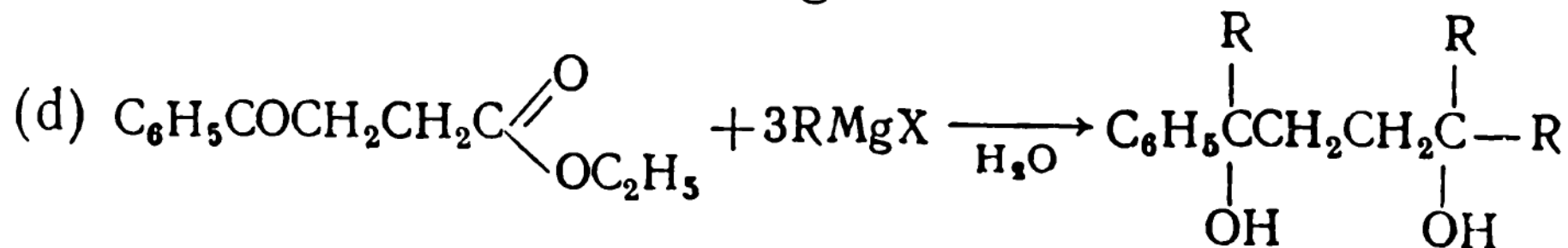
(l) Acetylacetone + RMgX → enolization (see 65 and 66),
3-bromobut-1-ene + RMgX → see 14.

(m) The reaction of calcium acetate, like that of other salts of carboxylic acids, cannot be stopped at the stage of formation of a ketone (see 48) since the corresponding tertiary alcohol will always be formed.

3-Bromo-2-methylprop-1-ene + RMgX → see 14; triacetyl-methane + RMgX → enolization (see 65, 66).

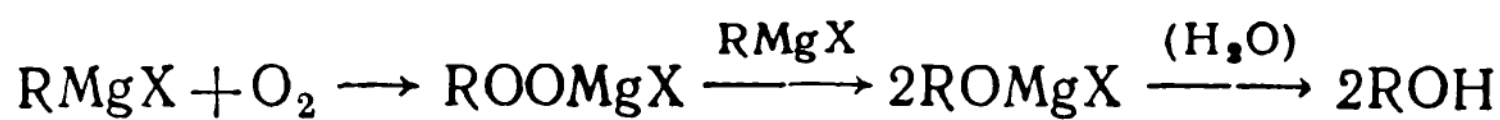


orthocarbonate + excess of RMgX → see 53.



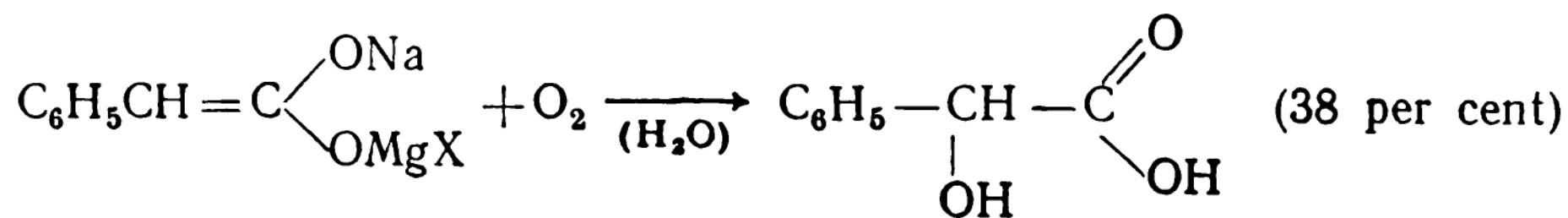
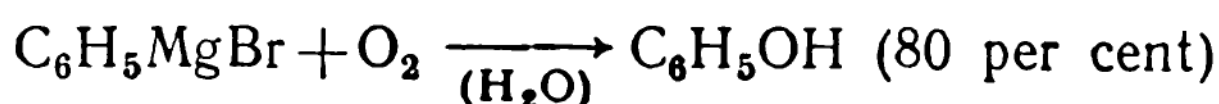
a complex with ether and is found to bear a certain resemblance to Grignard reagents.

It is usually believed that organomagnesium compounds react with oxygen according to the following scheme:



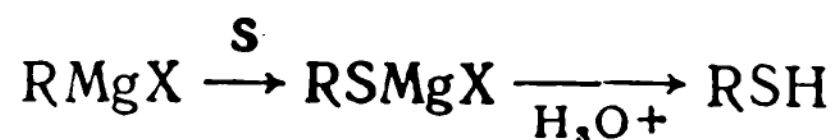
The preparation of alcohols by oxidation of Grignard reagents is however often complicated by various side processes, which is probably explained by the formation of peroxides (and, naturally, of radicals from them) in the course of oxidation.

In some cases when pure dry oxygen is used, this reaction may be of preparative value:



(see Problem 65).

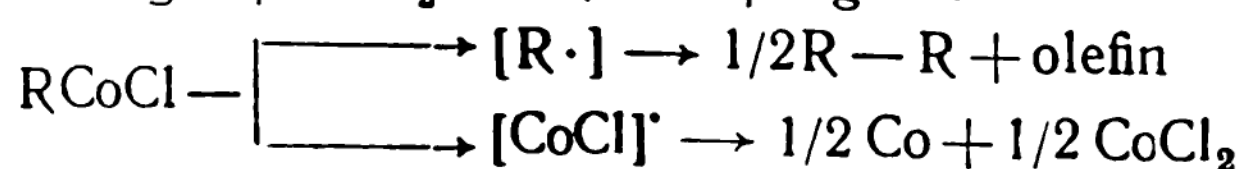
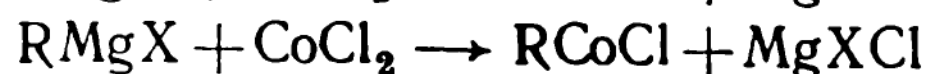
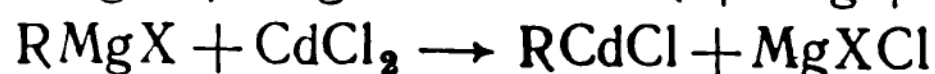
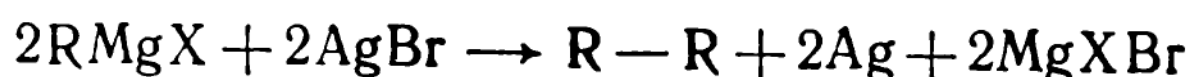
(b) The reaction of organomagnesium compounds with sulphur is carried out in a current of dry nitrogen; it leads to mercaptides, from which mercaptans can be made:

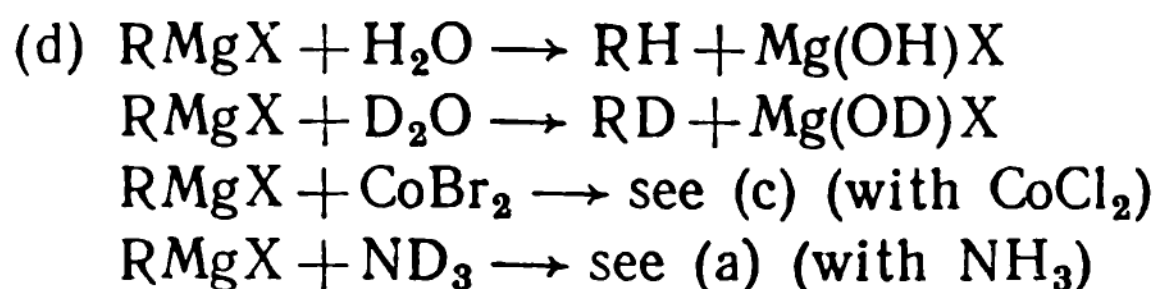


To avoid the formation of disulphides, use must be made of a somewhat smaller quantity of sulphur than is required by the equation of the reaction.

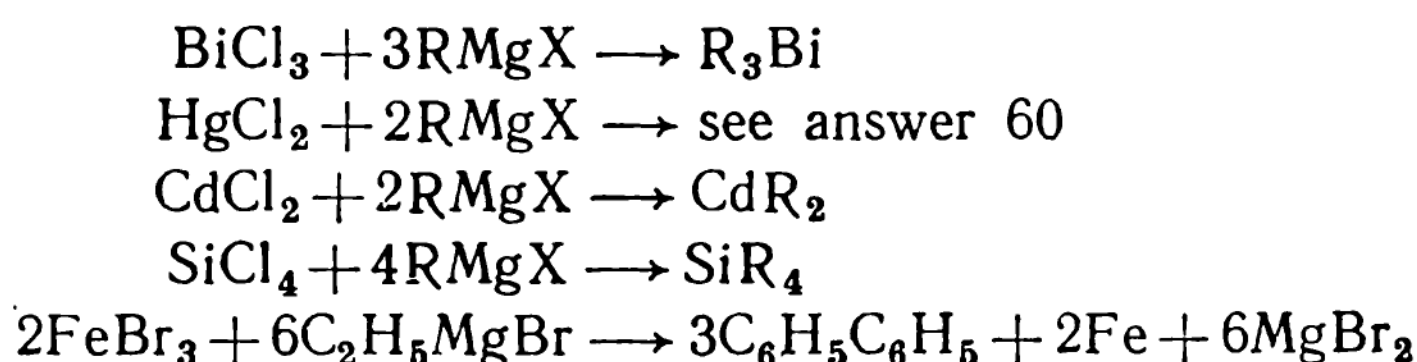
For the interaction of RMgX with iodine see answers 55 and 56; and with phosphorus trichloride and mercuric chloride—answer 60.

(c) Gaseous dry hydrogen bromide and chloride do not react with organomagnesium compounds

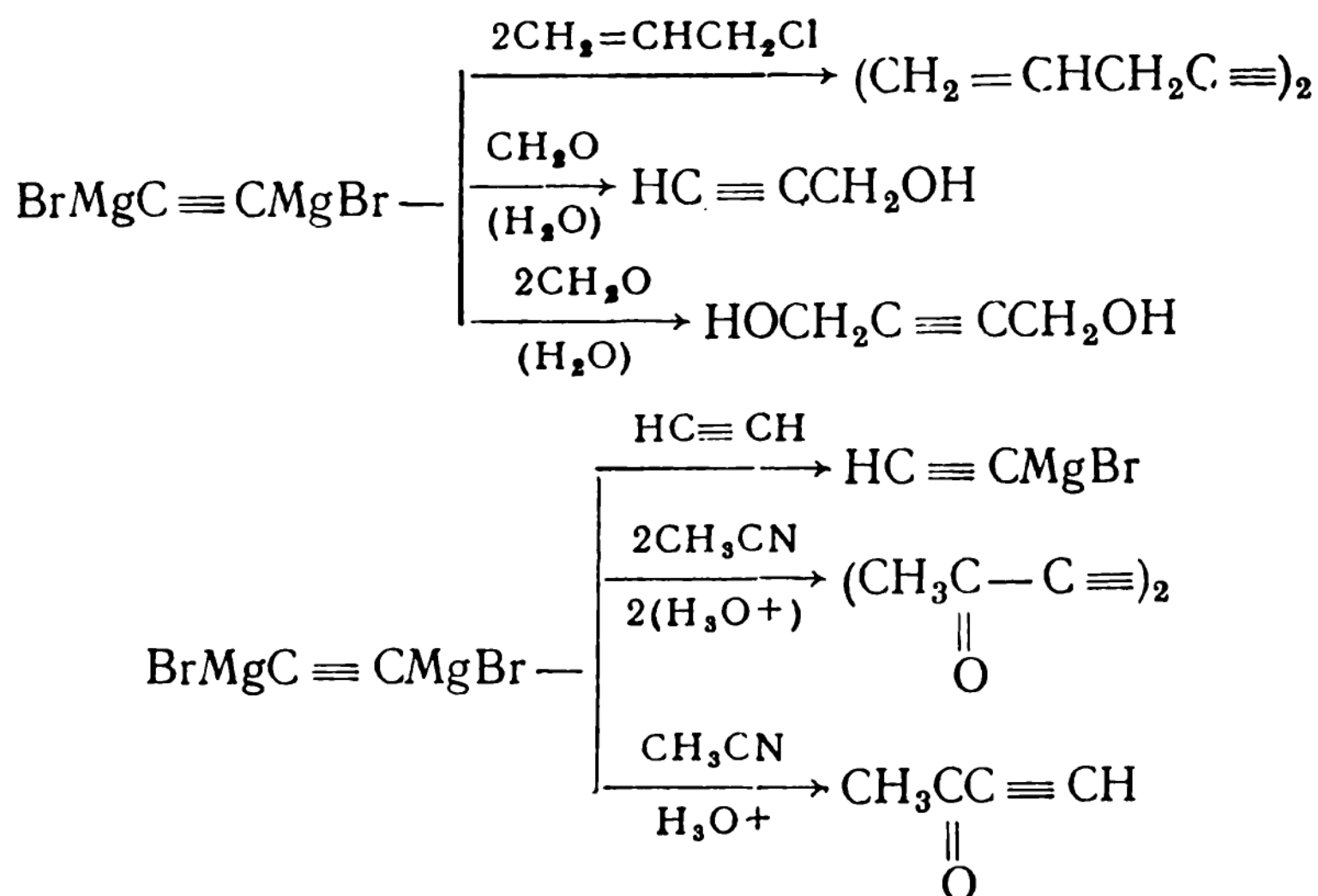




72. Under ordinary conditions only one molecule of an organomagnesium compound reacts with one molecule of ammonia (see answer 71):



73.



75. I—diethyl ketone; II—3-ethylpent-2-ene.

76. A—*tert*-butylacetylene; B—2,2,3,6,6-pentamethylhept-4-yn-3-ol.

77. A—pent-1-en-4-ol containing 2-methylbut-3-en-1-ol as an impurity; B—propionates of the alcohols indicated.

78. Ethylmagnesium bromide.

79. Methyl ethyl ketone.

80. Acetonitrile.

81. Propionic acid.

82. (a) When propylene is subjected to allyl chlorination, allyl chloride is formed. The addition of hydrogen bromide to propylene under the conditions of a radical reaction

(contrary to Markovnikov's rule) leads to *n*-propyl bromide, which then gives propylmagnesium bromide. The last-named compound and the allyl chloride obtained earlier are used in the Grignard-Wurtz reaction to obtain hex-1-ene, from which by addition of bromine and cleavage of two molecules of hydrogen bromide there is prepared hex-1-yne. This compound is converted by the action of propylmagnesium bromide into hex-1-ynemagnesium bromide, which when subjected to the action of carbon dioxide and to ordinary hydrolysis gives hept-2-ynoic acid.

From propylene by the route described above there is obtained allyl chloride, which when subjected to the action of magnesium in ether gives diallyl. To this compound are added two moles of hydrogen bromide (in accord with Markovnikov's rule) and dibromide is converted into a dimagnesium derivative, which is subjected to carbonization (the action of CO_2) to form 2,5-dimethyladipic acid.

(b) By the route described above propylene gives propylmagnesium bromide, which by reaction with acetone (obtained from propylene via isopropyl alcohol) gives 2-methylpentan-2-ol.

To prepare heptan-4-one, propyl bromide is converted by the action of potassium cyanide into butyronitrile, which is brought into reaction with propylmagnesium bromide.

(c) Acetylene is converted by the Kucherov reaction into acetaldehyde, which is reduced to ethyl alcohol. The subsequent conversions are as follows: ethyl alcohol $\rightarrow$ ethyl bromide $\rightarrow$ ethylmagnesium bromide. By the action of the last-named compound on acetylene there is obtained the Iotsich complex, which is carbonized to give acetylenedicarboxylic acid.

To prepare 2,5-dimethylhexyne-2,5-diol the Iotsich complex is brought into reaction with acetone made from acetylene via acetaldehyde and acetic acid.

(d) From but-1-ene there is obtained but-1-yne (see answer to Problem 82, a), which on hydration under the conditions of the Kucherov reaction gives methyl ethyl ketone. The reaction of methyl ethyl ketone with butylmagnesium bromide (made from but-1-ene by addition of hydrogen bromide contrary to Markovnikov's rule and by the action of magnesium) leads to 3-methylheptan-3-ol.

3-Methylhept-4-yn-3-ol is made by reaction of methyl ethyl ketone with but-1-ynemagnesium bromide obtained from but-1-yne and butylmagnesium bromide.

(e) Dibenzylacetic acid is made as follows. Toluene is chlorinated into the side chain to benzyl chloride, which is converted via an organomagnesium compound into phenylacetic acid. The catalytic ketonization of phenylacetic acid over manganous oxide leads to dibenzyl ketone, which is reduced to dibenzylcarbinol. The last-named compound is converted into the corresponding bromide from which an organomagnesium compound is made, which is then subjected to the action of carbon dioxide.

(f) The route from acetylene to dimethylethylcarbinol is via acetaldehyde, from which there are obtained acetone (via acetic acid) and ethylmagnesium bromide (via ethanol and ethyl bromide). The interaction of these reagents yields the required alcohol.

To prepare 2,5-dimethylhex-3-yne-2,5-diol from acetylene and ethylmagnesium bromide, the Iotsich complex is made, which is introduced into the reaction with acetone.

(g) Acetylene is a starting material for preparing ethylmagnesium bromide, acetaldehyde, acetone and the Iotsich complex (see the previous answer). Toluene is used to prepare benzyl chloride and benzylmagnesium chloride. The latter is reacted with acetone to give dimethylbenzylcarbinol; by reaction with acetaldehyde it gives methylbenzylcarbinol, which is oxidized to form benzyl methyl ketone (phenylacetone). The action of ethylmagnesium bromide on phenylacetone gives methylethylbenzylcarbinol, and from the Iotsich complex and phenylacetone there is obtained 2,5-dimethyl-1,6-diphenylhex-3-yne-2,5-diol.

(h) Methanol is converted by oxidation into formic acid, which is used to make its methyl ester. The reaction of this compound with methylmagnesium iodide (made from methanol via methyl iodide) leads to the formation of isopropyl alcohol. Isopropyl alcohol is converted via the corresponding bromide into an organomagnesium compound, which by reaction with methyl formate gives diisopropylcarbinol. This compound is converted into a bromide and then into an organomagnesium compound, which is subjected to carbonization to yield diisopropylacetic acid. The dehydration of isopropyl

alcohol gives propylene, from which is synthesized, by addition of hydrogen bromide contrary to Markovnikov's rule, propyl bromide, and then by allyl chlorination, allyl chloride. Propyl bromide is converted into propylmagnesium bromide, which by reaction with methyl formate and subsequent oxidation gives di-*n*-propyl ketone. The reaction of allyl chloride with magnesium and acetone yields dimethylallylcarbinol.

(i) Ethanol is converted via ethyl bromide and ethylmagnesium bromide (or propionitrile) into propionic acid. The reaction of its ester with ethylmagnesium bromide gives triethylcarbinol. Having obtained acetic acid and then acetone from ethanol, dimethylethylcarbinol is made by reaction with ethylmagnesium bromide. *n*-Butanol is made by dehydration of ethyl alcohol as follows: ethyl alcohol is dehydrated and the resulting ethylene is converted into ethylene oxide, which is allowed to react with ethylmagnesium bromide.

(j) Propan-1-ol is oxidized to propionic acid. From propionic acid there is obtained an amide, which is dehydrated to give propionitrile. The reaction of propionitrile with propylmagnesium bromide yields ethyl propyl ketone.

The dehydration of propan-1-ol leads to propylene, from which by addition of hydrogen bromide there is prepared isopropyl bromide and then isopropylmagnesium bromide and isobutyric acid. The reduction of the last-named compound by lithium aluminium hydride results in the formation of isobutyl alcohol. When isobutyl alcohol is dehydrated, isobutylene is formed, which is then subjected to allyl chlorination to yield methallyl chloride. The reaction of the latter compound with magnesium and ethyl propyl ketone gives 2-methyl-4-ethylhept-1-en-4-ol.

(k) Butan-1-ol is converted into butyl bromide, which serves as a starting material for preparation of butylmagnesium bromide and *n*-valeronitrile. The last two compounds are then converted into dibutyl ketone. When dibutyl ketone is again made to react with butylmagnesium bromide, tri-*n*-butylcarbinol is formed.

(l) Isoamyl alcohol is converted via isoamylenes and the corresponding dibromide into 3-methylbut-1-yne, which is subjected to the action of isoamylmagnesium bromide to give an organomagnesium compound. The carbonization

of the resulting acetylene organomagnesium compound gives 4-methylpentyn-2-oic acid, which is esterified by isoamyl alcohol.

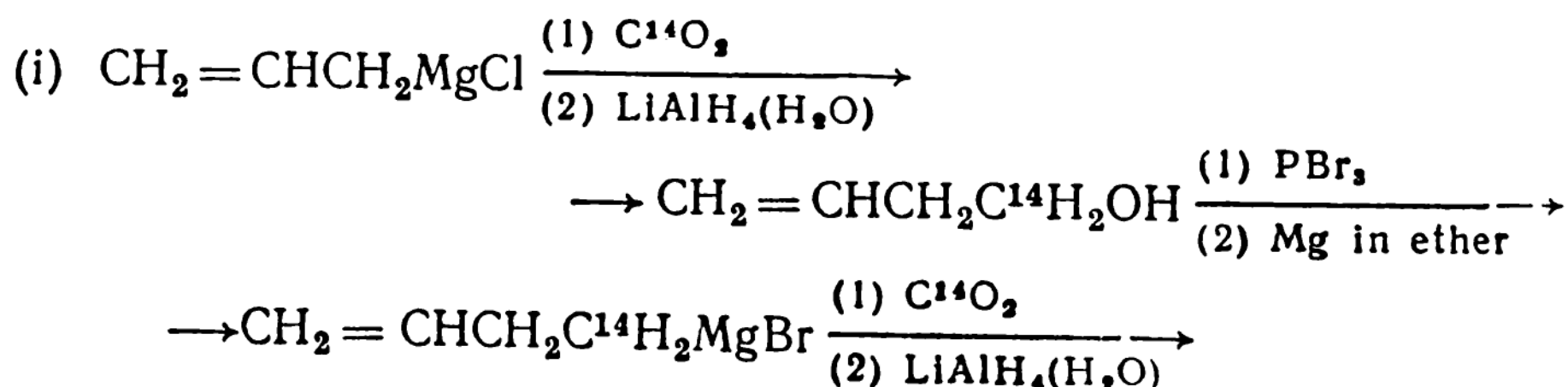
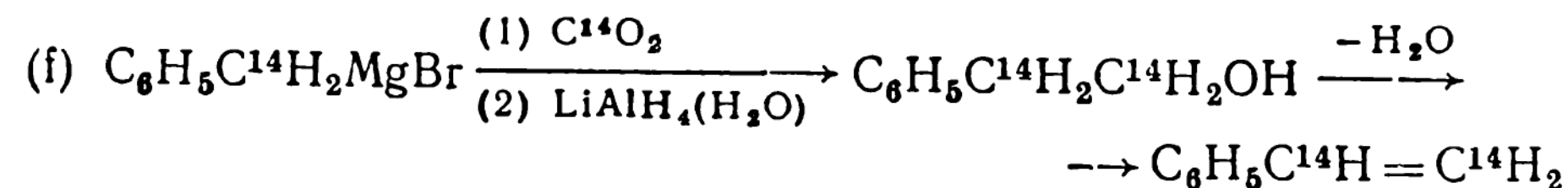
(n) The oxidation of cyclohexanol leads to adipic acid, which is converted into an acid chloride. The acid chloride is reduced to hexane-1,6-dial by the Rosenmund reduction. The reaction between this dialdehyde and cyclohexylmagnesium bromide results in the formation of 1,6-dicyclohexylhexane-1,6-diol. From cyclohexylmagnesium bromide and carbon dioxide there is obtained cyclohexanecarboxylic acid and from the calcium salt of this acid, dicyclohexyl ketone. The reduction of the last-named compound to an alcohol with subsequent conversion into a bromide and then into an organomagnesium compound, which is subjected to carbonization, gives dicyclohexylacetic acid.

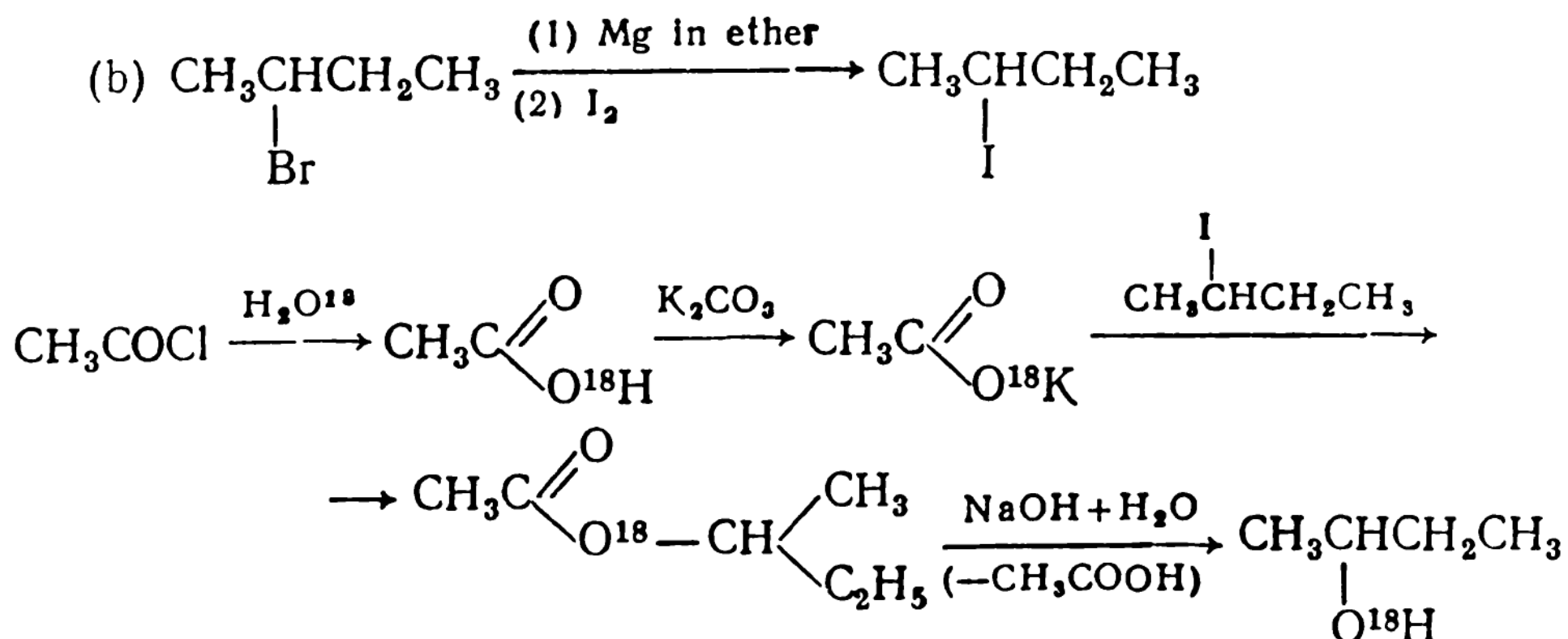
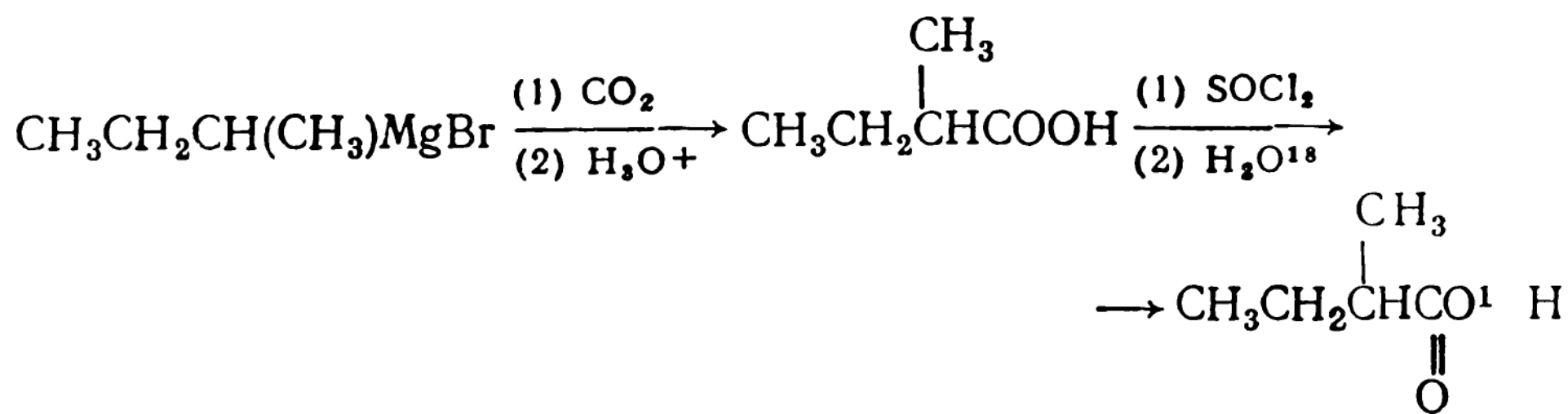
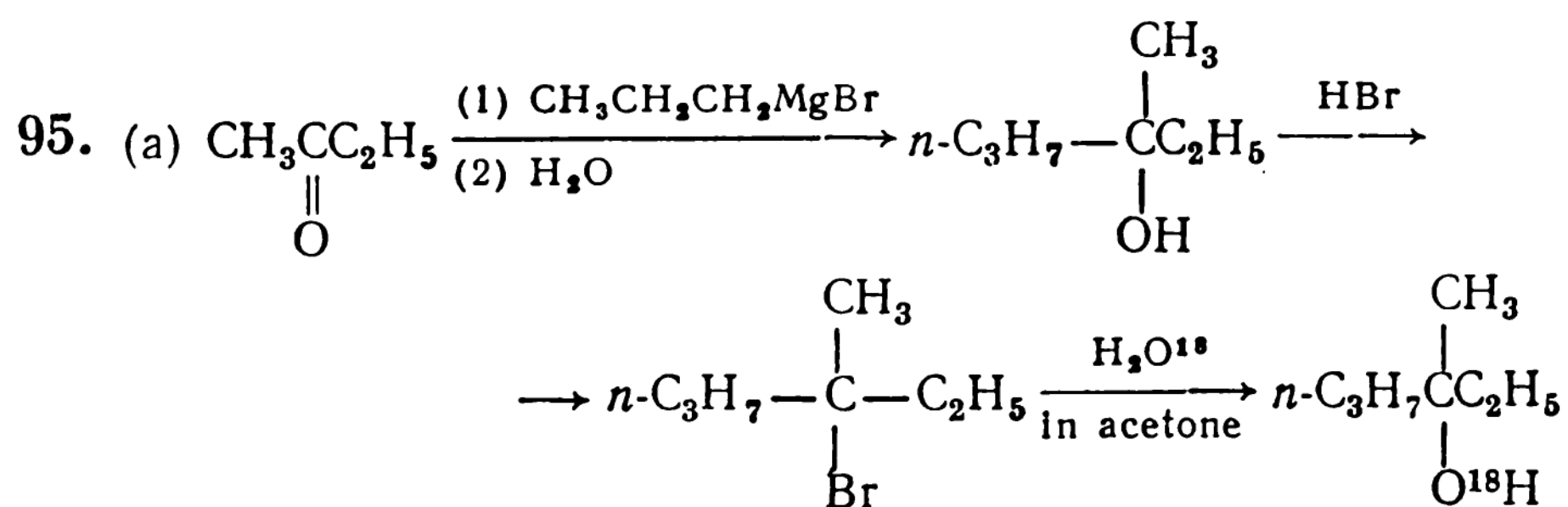
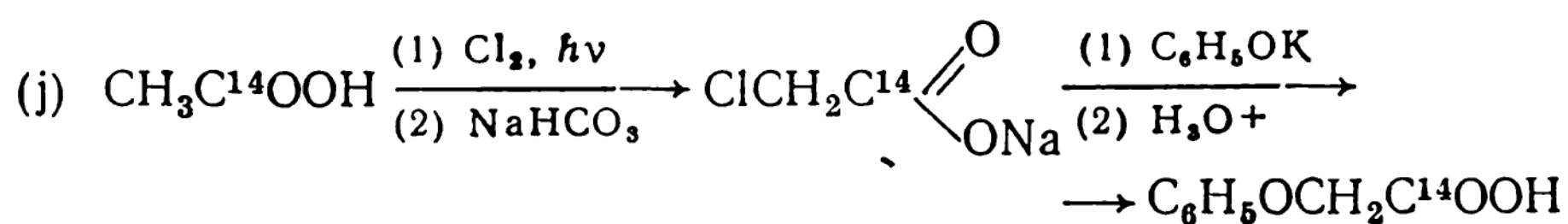
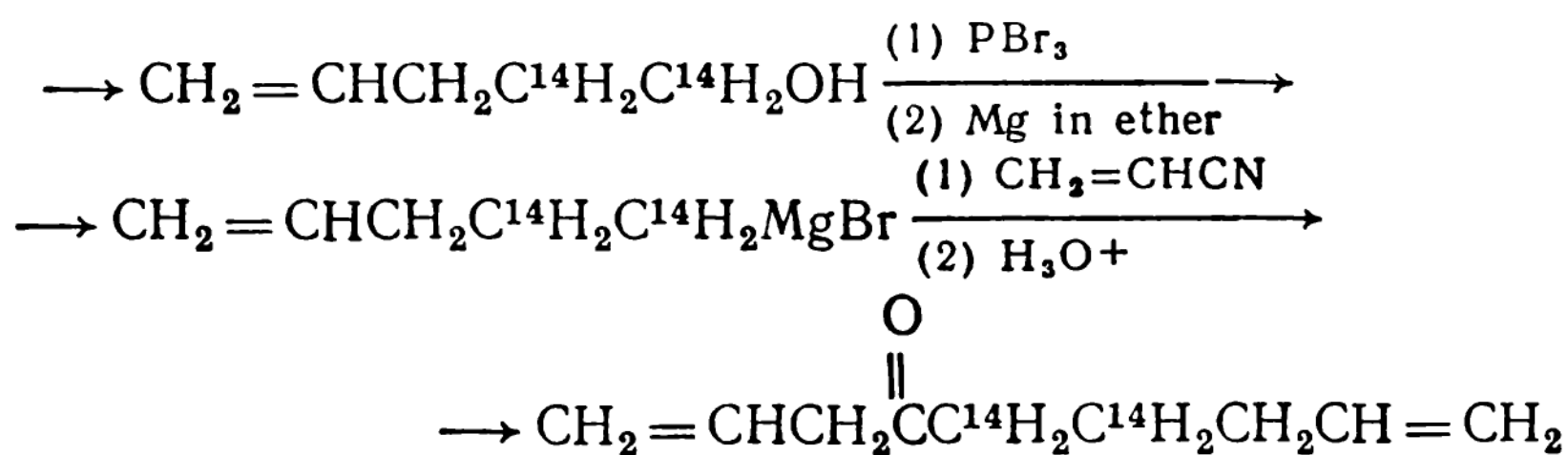
(o) The key substances for the syntheses are ethyl formate (made by partial saponification of orthoformic ester), methylmagnesium iodide (via methanol obtained by reduction of formic acid—the product of saponification of orthoformic ester) and ethylmagnesium bromide (via ethanol made from the same ester). Ethyl formate when reacting with two moles of methylmagnesium iodide gives isopropyl alcohol, which is then converted into the corresponding bromide and then into an organomagnesium compound. When the last-named compound reacts with orthoformic ester, isobutyraldehyde diethyl acetal is formed. By reaction with orthoformic ester ethylmagnesium bromide (1 mole) forms propionaldehyde. The reaction between two moles of ethylmagnesium bromide and ethyl formate yields diethylcarbinol, which is subjected to the action of hydrogen bromide, magnesium and orthoformic ester to give 2-ethylbutanal.

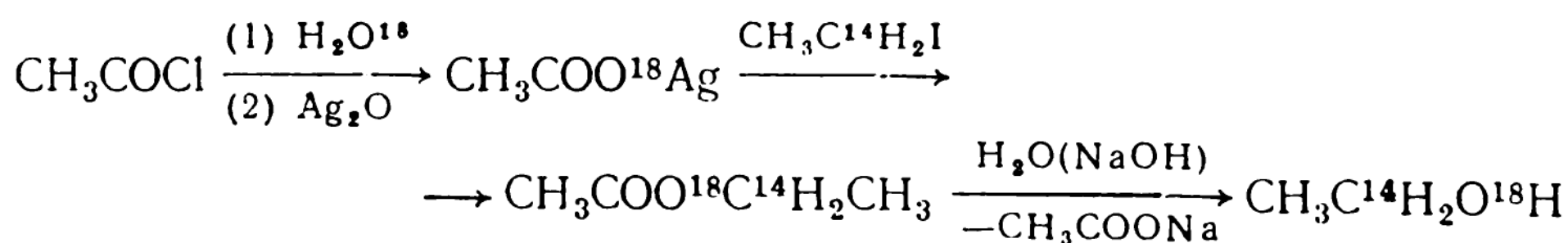
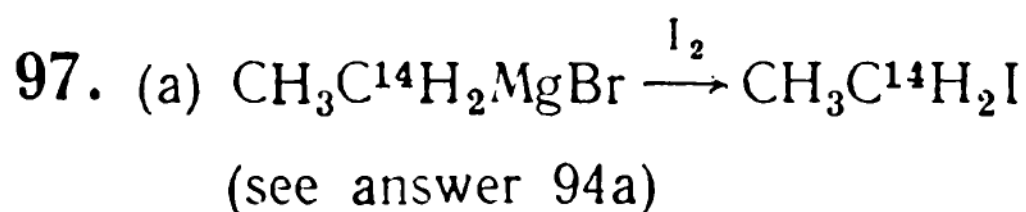
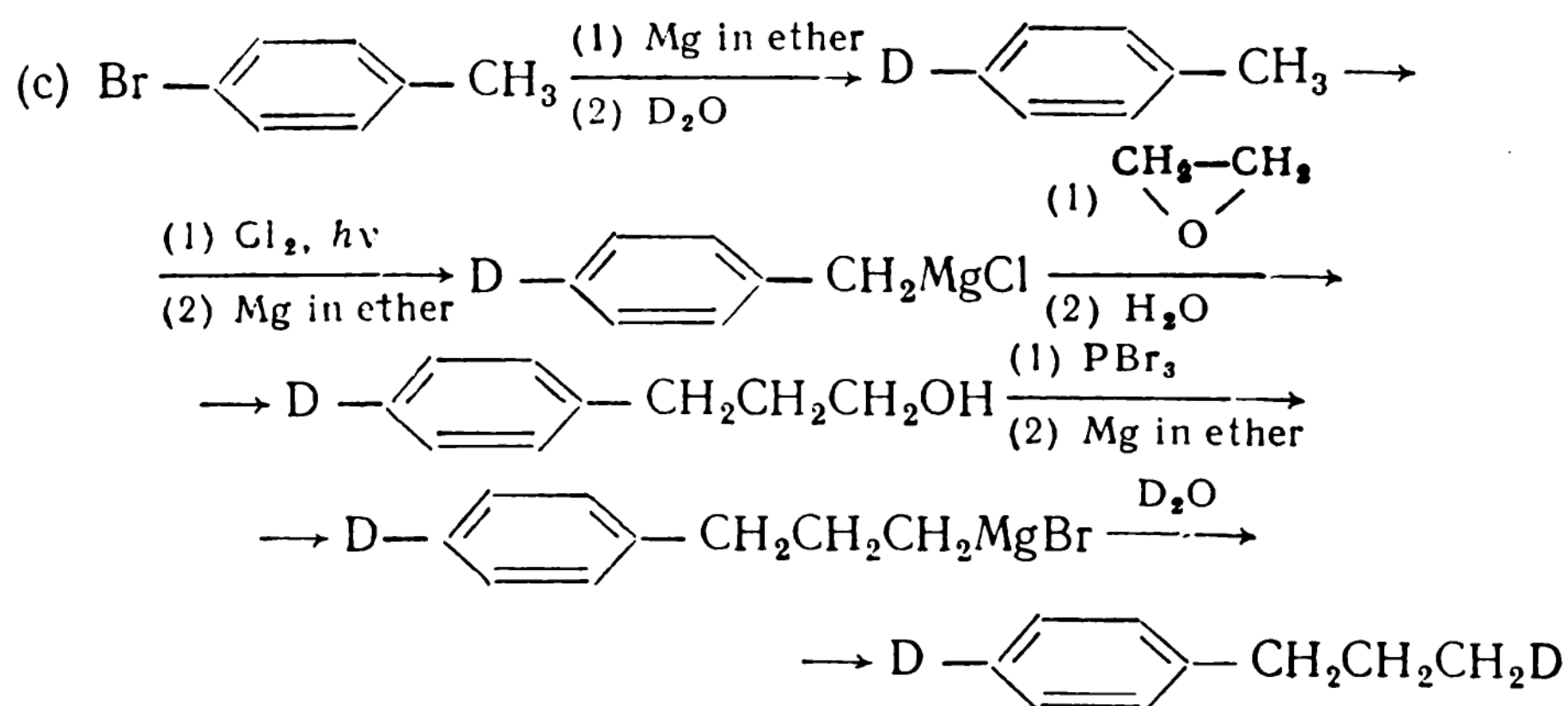
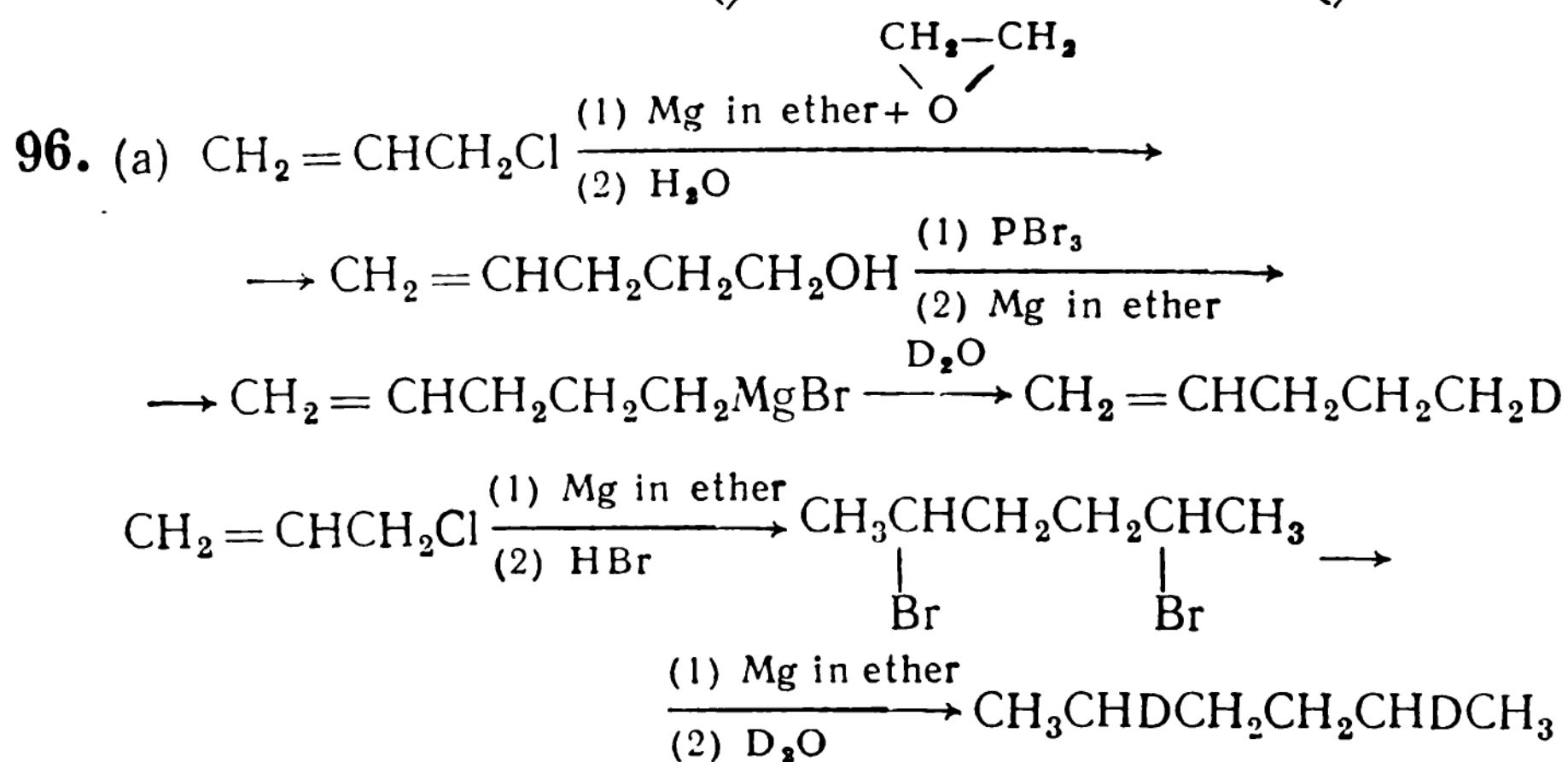
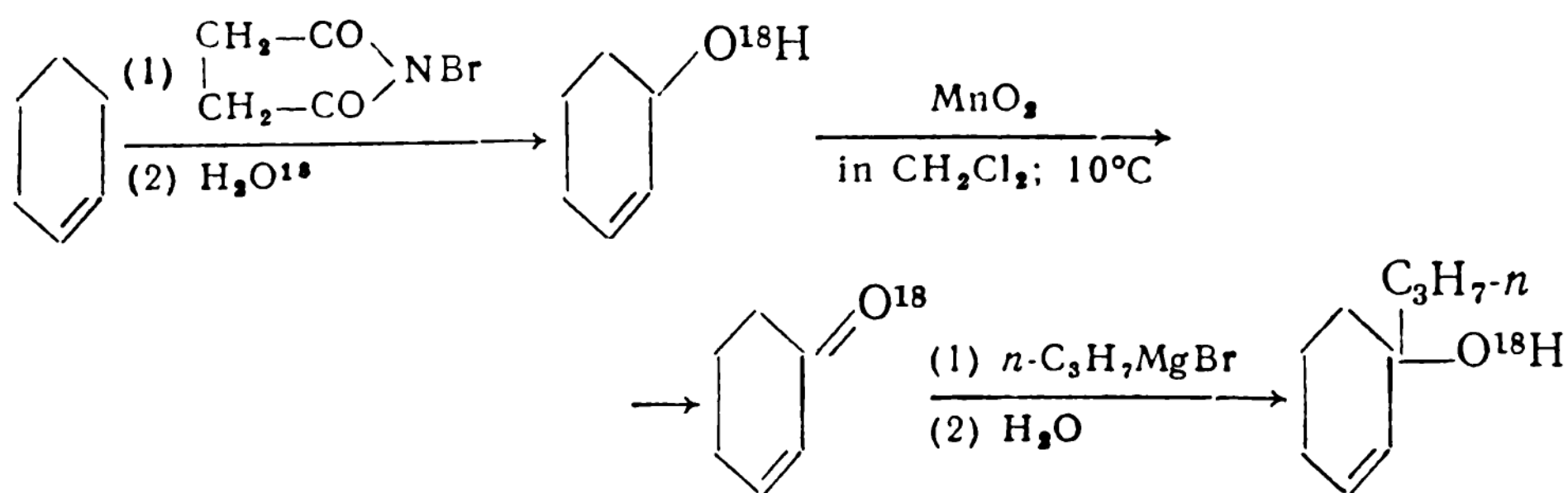
(r) Adipic acid is esterified and the diester formed is subjected to the Dieckmann cyclization reaction and decarboxylation. The resulting cyclopentanone is brought into reaction with methylmagnesium iodide.

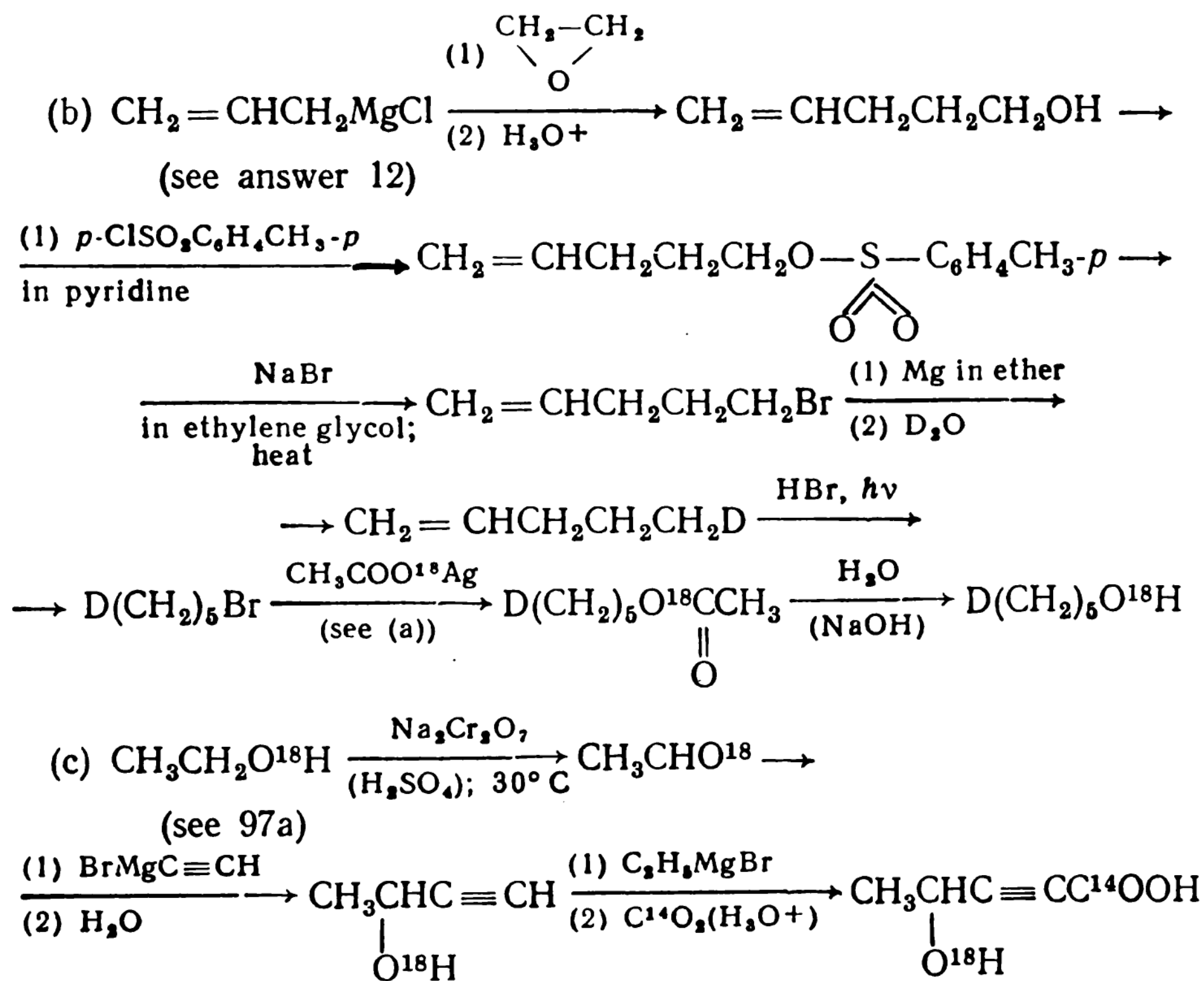
(s) Acetone is converted via isopropyl alcohol and a bromide into isopropylmagnesium bromide, which by reaction with propyne (obtained from acetone by the action of phosphorus pentachloride and then of alkali) gives propynemagnesium bromide. When this compound reacts with acetone, 2-methylpent-3-yn-2-ol is formed.

- E









CHAPTER 7

SUBSTITUTION REACTIONS IN THE AROMATIC NUCLEUS

In a general course of organic chemistry, aromatic compounds are treated, as a rule, separately from other unsaturated compounds. This is explained by the fact that the properties of these aromatic compounds differ sharply from those of both non-conjugated and conjugated polyenes of the aliphatic and alicyclic series. The concept of "aromatic" compounds has greatly changed and at present it embraces a variety of carbo- and heterocyclic and "sandwich" (for example, ferrocene) systems.

The chemical properties of aromatic compounds have been studied rather extensively, and sufficiently thoroughly in many cases. The available experimental data have made it possible to formulate the concepts of the mechanism of many conversions of aromatic compounds.

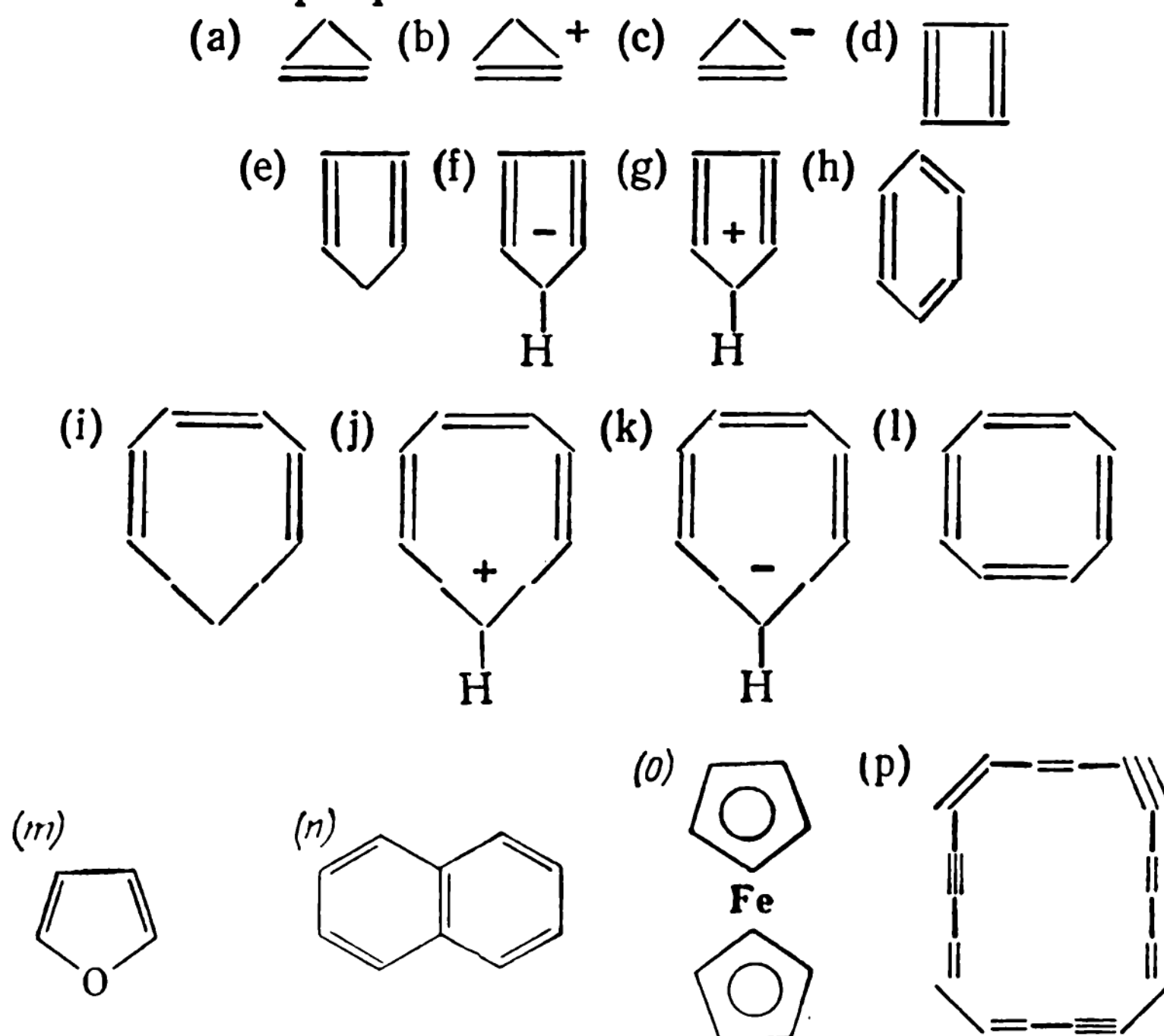
The material concerning the properties of aromatic compounds may be found in A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 2, Moscow, Khimiya, 1970, and J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

The present chapter covers problems and exercises dealing with the general conceptions of electrophilic and nucleophilic reactions, methods of generation of electrophilic reagents, the orientation of substitution reactions and the acidity or basicity of phenols, aromatic carboxylic acids and amines. Besides, problems are given, the solution of which requires the use of general theoretical concepts for synthetic purposes.

Problems and Exercises

1. GENERAL CONCEPTS OF ELECTROPHILIC SUBSTITUTION

1*. Which of the following species may be expected to exhibit aromatic properties:



Define the concept of an aromatic compound.

2*. Suggest structures for hydrocarbons A and B given that they both are of the general formula C_6H_6 , hydrocarbon A immediately renders bromine water and a solution of potassium permanganate colourless; hydrocarbon B is inert with respect to these reagents; neither hydrocarbon reacts with a solution of silver nitrate.

3*. What reagents could be used as electrophiles in reactions of electrophilic substitution?

4*. What methods are employed for generation of electrophilic reagents in the following reactions: (a) halogenation; (b) nitration; (c) sulphonation; (d) Friedel-Crafts reaction; (e) Vilsmeier reaction; (f) Reimer-Tiemann reaction; (g) Gattermann reaction?

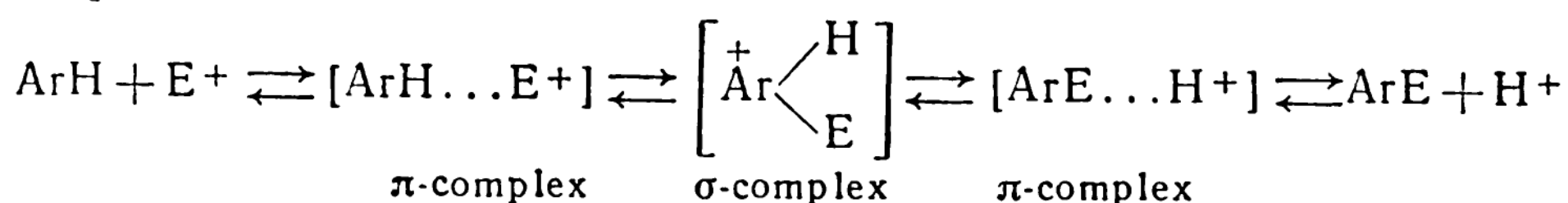
5. What methods of enhancing and diminishing the electrophilicity of a reagent do you know?

6. Many electrophilic reagents exhibit oxidizing properties in reactions with aromatic compounds. Such oxidation reactions proceed especially easily for arenes possessing enhanced nucleophilicity (give examples of such compounds). What methods of reducing the nucleophilicity of an aromatic substrate do you know?

7*. It is known that toluene is capable of forming with HCl reversibly at -78°C a colourless complex of the composition 1 : 1. Suggest a structure for this complex given that when, instead of HCl, use is made of its deuterium analogue, no deuterium exchange occurs and the solution of this complex does not conduct electricity.

8*. The reaction of toluene with DCl in the presence of Lewis acids (for example, AlCl_3) leads to deuterotoluene (cf. the previous problem). Suggest a scheme for this reaction mechanism and give proofs in favour of the intermediate formation of σ -complex in this conversion and in other cases you know.

9*. It is generally believed that the electrophilic substitution in the aromatic series proceeds through the following steps:



What chemical data or physicochemical methods support this view on the mechanism of an electrophilic substitution reaction?

10*. It has been found that in the nitration of benzene, toluene, bromobenzene, nitrobenzene, and naphthalene, in whose molecules the hydrogen atoms are replaced by deuterium or tritium, the ratio of the velocities $K_{\text{H}}/K_{\text{T}}$ (or D) is, as a rule, very close to unity and usually does not exceed 3. What inferences could be made about the rate-determining step on the basis of the data given?

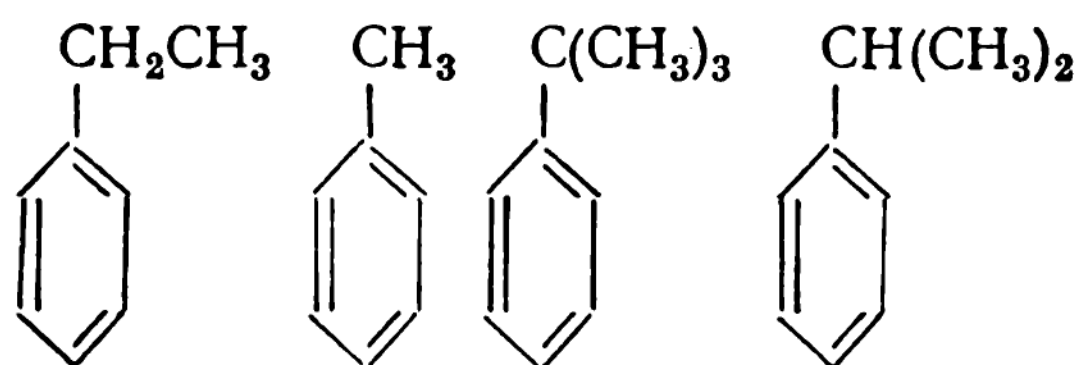
11. What factors govern the competition between the reactions of substitution and addition for aromatic compounds? What examples of substitution reactions proceeding via the addition-cleavage step do you know?

12*. How could benzene be converted into hexadeuterobenzene with the aid of electrophilic substitution reactions?

13. Phenol is known to engage more easily in reactions of electrophilic substitution than anisole. Explain this fact.

2. ORIENTATION IN ELECTROPHILIC SUBSTITUTION. RELATIVE REACTIVITY OF AROMATIC COMPOUNDS AND METHODS OF GENERATION OF ELECTROPHILIC REAGENTS

14*. In what sequence does the number of *para*-isomers increase in electrophilic substitution reactions for the following compounds:



15*. What nitrating agents are used for nitration of aromatic compounds? Discuss their advantages and limitations.

16*. Give experimental data supporting the intermediate formation of the nitronium cation in nitration reactions of aromatic compounds.

17. Write formulas for the nitronium cation, nitrite anion and nitrogen dioxide with account taken of their electronic structure. Compare their reactivities.

18*. Explain why the rate of nitration by concentrated nitric acid falls sharply on addition of salts of nitric acid (for example, sodium nitrate) and increases on addition of concentrated sulphuric acid.

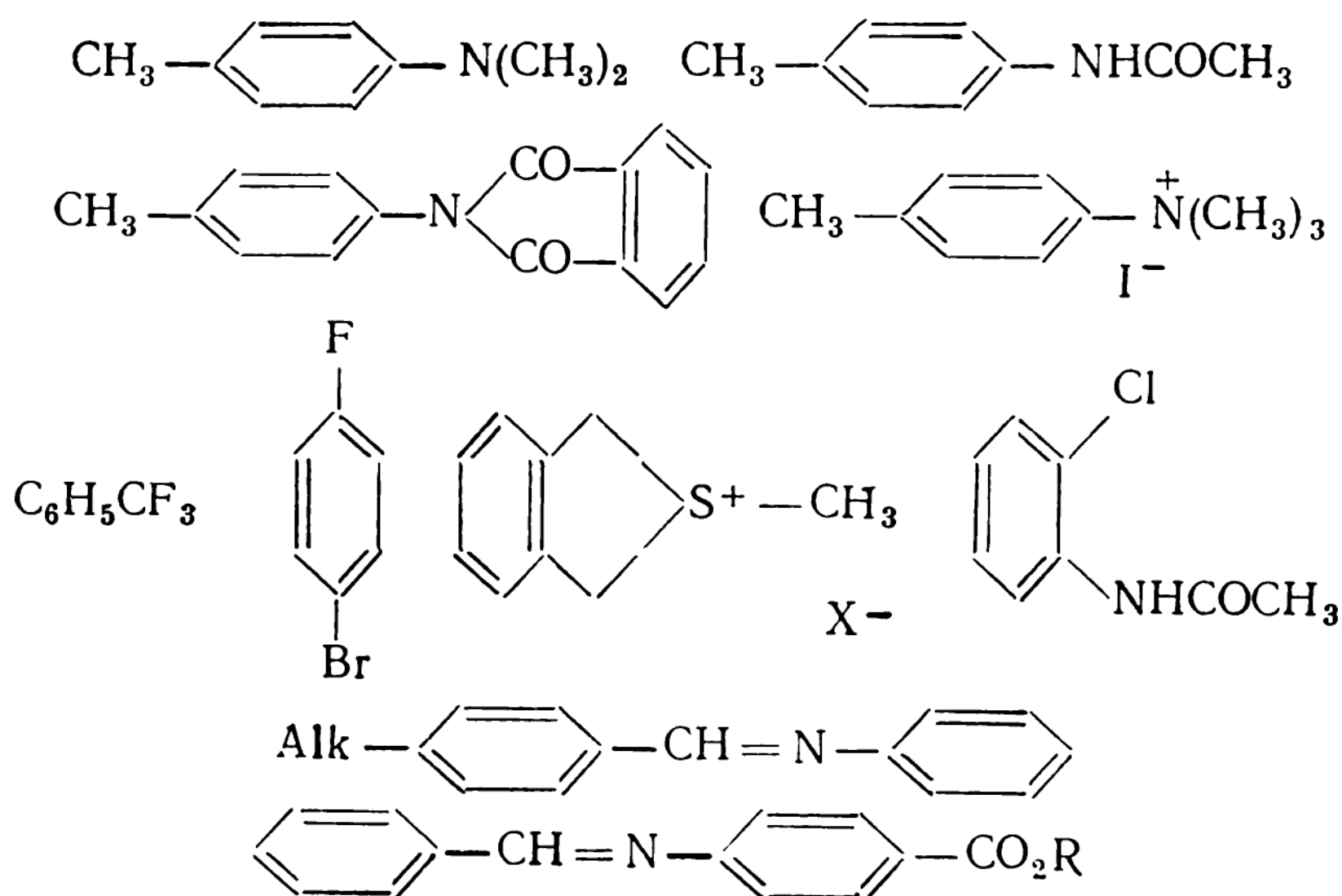
19. It is known that on nitration of some aromatic compounds under certain conditions the reaction rate is independent of the concentration and nature of an aromatic compound. Does it mean that if the nitration of a mixture of benzene and toluene is stopped under given conditions the quantities of benzene and toluene that have reacted will be equal? Can it be inferred on the basis of the data given that in such cases the rate-determining step is the generation of the nitronium cation? Explain why the rate of nitration of *p*-dichloroben-

zene under the same conditions is proportional to the concentration of the aromatic compound.

20*. What side reactions are observed in the nitration of aromatic compounds?

21. The nitration of veratrole (1,2-dimethoxybenzene) leads to the formation of a compound having the general formula $C_8H_8N_2O_6$. Suggest a structure for this reaction product.

22. What reaction products can be formed in the nitration of the following compounds:



23. Predict the structures of the products resulting from the nitration of the following compounds. Arrange the compounds indicated in order of increasing rate of their nitration:

(a) *p*-bromotoluene, *o*-chloroaniline, *m*-nitroanisole, *m*-hydroxybenzonitrile;

(b) *p*-chlorodimethylaniline, *o*-nitroethylbenzene, *m*-methylacetophenone, *p*-dichlorobenzene.

24. When benzaldehyde, nitrobenzene and acetophenone are nitrated, there are formed, together with *m*-nitro compounds, appreciable amounts of the corresponding *o*-isomers. Explain these results.

25. Predict the manner in which the ratio of *o*- and *p*-isomers will change in the nitration of benzene halides C_6H_5X , where $X = \text{F}, \text{Cl}, \text{Br}, \text{I}$. Consider the reactivity of the benzene halides in electrophilic substitution.

26. It is known that nitric acid is a rigorous oxidizing agent for various organic compounds (saturated and unsaturated hydrocarbons, alcohols, carbonyl compounds, etc.). Suggest conditions for nitration of benzaldehyde, in which its oxidation to benzoic acid would proceed to an insignificant degree.

27. The nitration of dimethylaniline in concentrated sulphuric acid results largely in the formation of two mononitro derivatives. How does the ratio of these compounds depend on the concentration of sulphuric acid? How could you separate a mixture of these substances by using the difference in the basicity of the starting dimethylaniline and the reaction products?

28. It is known that arylsulphonic acids, and their sodium and barium salts are well soluble in water. Indicate methods of separating and identifying arylsulphonic acids.

29. Suggest a method for preparing *o*-chloroaniline and 2,6-dinitroaniline from aniline.

30. Benzene obtained from coal tar gives a so-called indophenine reaction (the mixing of crude benzene, isatine, and concentrated acid results in the appearance of a blue-green colour). At the same time benzene resulting from the decarboxylation of benzoic acid does not give such a reaction. It has been established that the cause of the indophenine reaction is the presence of thiophene in coal benzene. Suggest a method (or methods) for separating thiophene from benzene (it should be kept in mind that the boiling points of thiophene and benzene are very close: 84° and 80.4°C, respectively). Write the schemes of the reactions suggested.

31. Suggest a method for chemical separation of a mixture of benzene and cyclohexane. Write equations for the reactions involved.

32*. The treatment of aniline sulphate with oleum gives *m*-aminobenzenesulphonic acid. When the same salt is heated (in a dry state) to 100-180°C, there occurs a substitution in the benzene ring at the *o*- and *p*-positions. How could the difference in these results be accounted for?

33. Predict the products of the sulphonation of *p*-bromoanisole, *p*-*tert*-butyltoluene, *m*-bromoaniline, and *p*-nitrobenzoic acid.

34. Suggest the structure of the products of sulphonation of the following compounds: *m*-nitrotoluene, *o*-bromophenol, *o*-bromoanisole, methyl *o*-nitrobenzoate, *p*-nitrotoluene, α -naphthylamine, and β -naphthol.

3. USE OF ELECTROPHILIC SUBSTITUTION REACTIONS FOR SYNTHETIC PURPOSES

35. What is the significance of the reversibility of a sulphonation reaction for synthesis of α - and β -naphthalene-sulphonic acids?

36. Suggest a method for preparing saccharin (the imide of *o*-sulphobenzoic acid) from toluene.

37. Suggest methods for preparing isomeric diatomic phenols.

38. Predict the result of the bromination of nitrobenzene if the ratios of the reagent used (nitrobenzene and bromine) are 1 : 1 and 1 : 2.

39. The chlorination of aromatic compounds with elemental chlorine is catalyzed by addition of small amounts of iodine. Suggest a scheme for such catalysis.

40. The reaction of anisole with bromine under mild conditions (20°C, dilution) leads to a mixture of the corresponding *ortho*- and *para*-isomers. If dioxane-dibromide is used instead of bromine under the same conditions, only *para*-isomer is formed. How can this difference be accounted for?

41. Which of the following compounds undergoes bromination with elemental bromine most readily: chlorobenzene, acetanilide, benzenesulphonic acid, methyl benzoate?

42. What reagents can be used on introduction of a halogen into molecules of aromatic compounds? Give examples of the directed halogenation of aromatic compounds.

43. Why does the action of excess bromine water on phenol lead to the formation of tetrabromophenol with further substitution being stopped? Compare the structure of the σ -complex formed in the bromination of phenol with that of tetrabromophenol. What properties must this substance possess?

44. Using the Reimer-Tiemann reaction, prepare vanillin (4-hydroxy-3-methoxy-benzaldehyde) from pyrocatechol and other reagents. Consider the structure and the route of sta-

bilization of the σ -complex in this reaction (compare with the σ -complex obtained in the bromination of phenol).

45. What is the mechanism of the action of catalysts in the Friedel-Crafts reaction? What requirements must the catalysts used in this reaction satisfy?

Name the compounds formed in the alkylation of benzene by methallyl chloride (1-chloro-2-methylprop-2-ene) in the presence of concentrated sulphuric acid and aluminium chloride.

46. The alkylation of benzene with isobutyl bromide by the Friedel-Crafts reaction leads to *tert*-butylbenzene. Suggest the mechanism of this conversion. How can isobutylbenzene be obtained?

47*. The acylation of toluene with trimethylacetylchloride in a solution of carbon sulphide in the presence of AlCl_3 is accompanied by the side reaction of decarboxylation of the acid chloride and formation of *tert*-butyltoluene. This side reaction is the more pronounced the greater is the degree of dilution of the reaction mixture. Explain these facts.

48. Give an explanation for the following experimental data: no isomerization of the alkyl group takes place in the alkylation by the Friedel-Crafts mechanism with the aid of *tert*-butyl chloride, whereas in the alkylation by means of 2-chloro-2-methylbutane the isomerization proceeds to a considerable extent.

49. What compounds could you expect to form in the acylation of tetraline, *o*-xylene, and pyrocatechol with acetyl chloride by the Friedel-Crafts mechanism?

50. Predict the structures of the products of the alkylation of benzene: (a) with but-2-en-1-ol in the presence of phosphoric acid; (b) with 2-methylbut-2-ene in the presence of sulphuric acid; (c) with neopentyl chloride in the presence of aluminium chloride.

51. Suggest routes for synthesis of the following compounds from benzene and inorganic reagents: (a) isomeric hydroxybenzoic acids; (b) isomeric nitrophenols; (c) isomeric dihydroxybenzenes; (d) *o*-bromophenols; (e) *p*-hydroxybenzophenone; (f) *p*-bromobenzoic acid; (g) β -benzoylacrylic acid.

52*. Using benzene, acetone, and inorganic reagents, suggest a route for synthesis of salicylaldehyde. What methods of preparing phenols do you know?

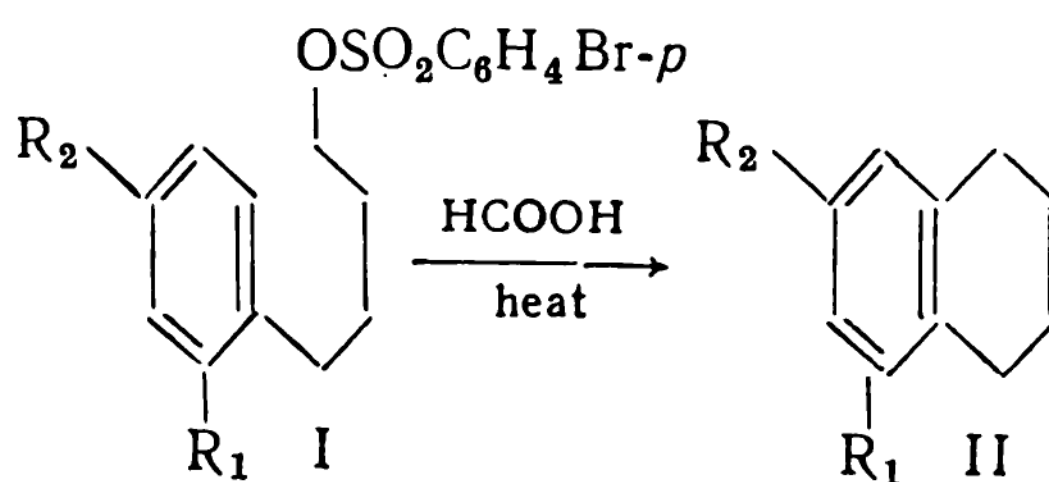
53*. How can *p*-diacetylbenzene and 2,5-diethylacetophenone be made from benzene and ethyl alcohol?

54. Give examples of the intramolecular alkylation and acylation by the Friedel-Crafts mechanism.

55*. Suggest routes for synthesis of the following compounds: 2,6-dichlorotoluene and 2-chloro-6-nitrotoluene from *p*-xylene; 2-naphthol-3,6-disulphonic acid, β -nitroso- α -naphthol, 1,8-naphthylenediamine, alizarine, α -aminoanthraquinone, α -naphthoic acid, α -nitroso- β -naphthol, α -nitro- β -naphthoic acid, and 3-nitrophthalic acid from naphthalene.

56. What side reactions are involved in the sulphonation of aromatic compounds? What measures are taken to prevent side reactions?

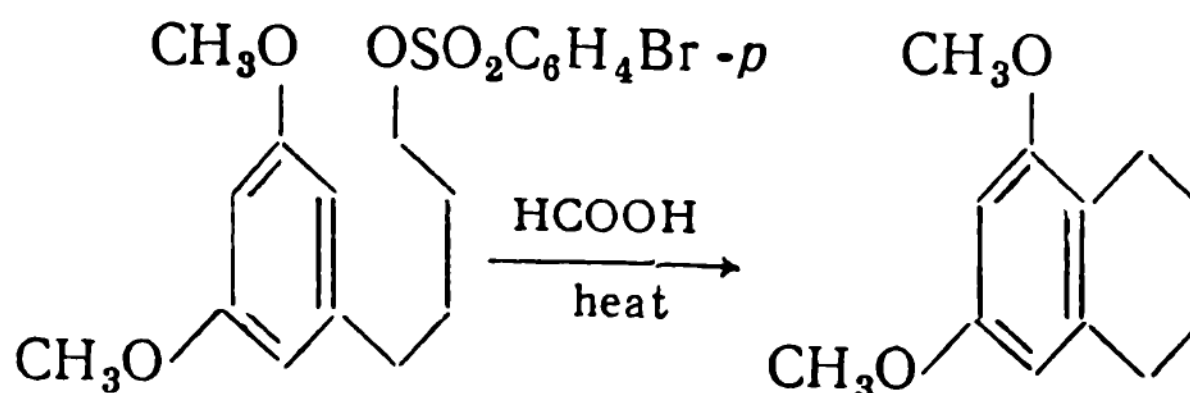
57. The heating of *p*-bromobenzene sulphonates of the general formula (I) in formic acid results in the formation of the corresponding tetralines (II):



- | | |
|--|--|
| (a) $R_1 = R_2 = \text{OCH}_3$ | (a) $R_1 = R_2 = \text{OCH}_3$ 76 per cent |
| (b) $R_1 = \text{H}, R_2 = \text{OCH}_3$ | (b) $R_1 = \text{H}, R_2 = \text{OCH}_3$ 51 per cent |
| (c) $R_1 = R_2 = \text{H}$ | (c) $R_1 = R_2 = \text{H}$ 16.5 per cent |

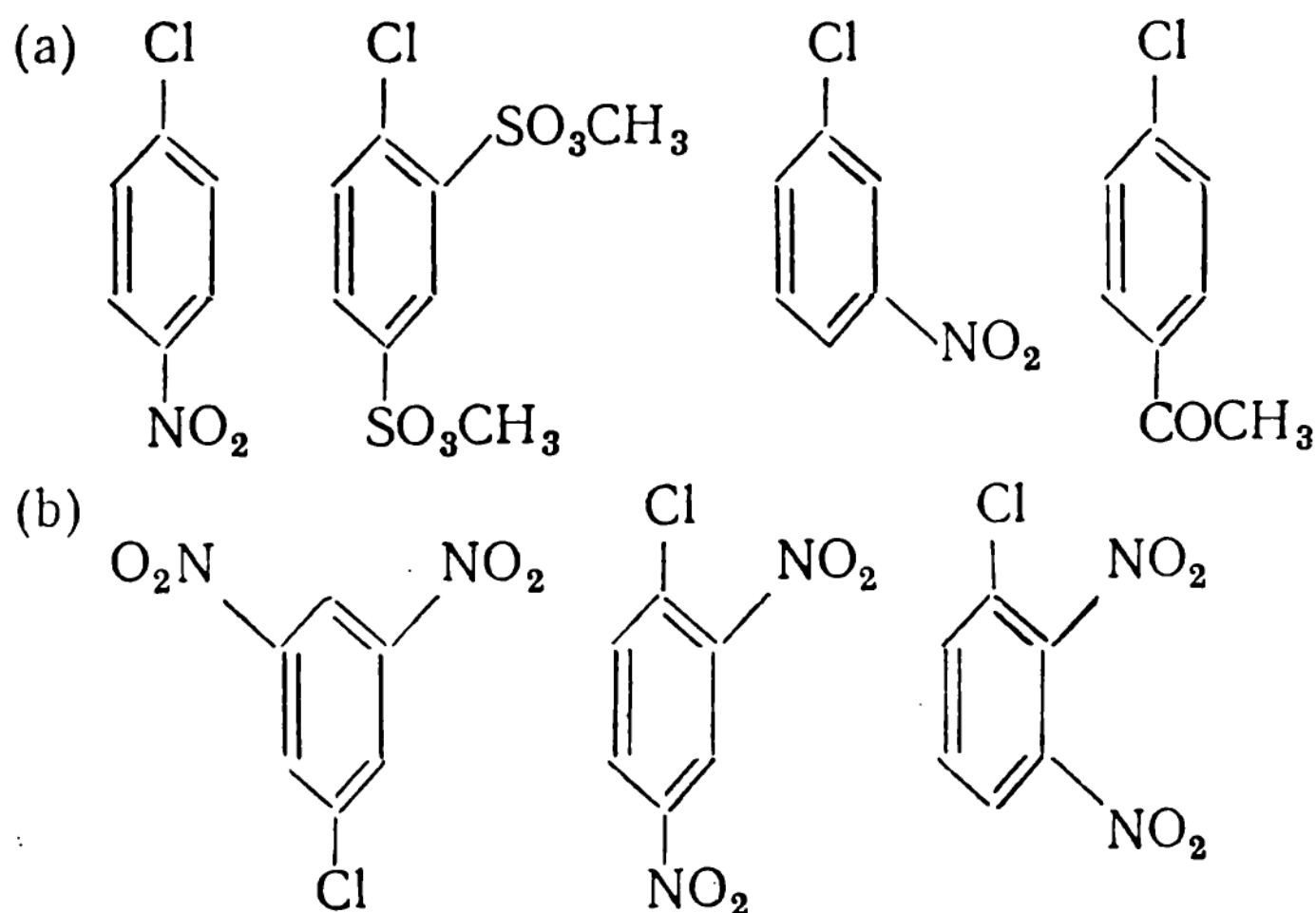
Suggest a possible scheme to account for this result. Why do the yields of the corresponding tetralines II,a-II,c decrease in going from I,a to I,c?

58. *p*-Bromobenzene sulphonate of 4-(3,5-dimethoxyphenyl)butanol when heated in formic acid gives 5,7-dimethoxytetraline. Explain why this reaction proceeds 6 times faster than the conversion of the corresponding derivative of 4-phenylbutanol into tetraline:

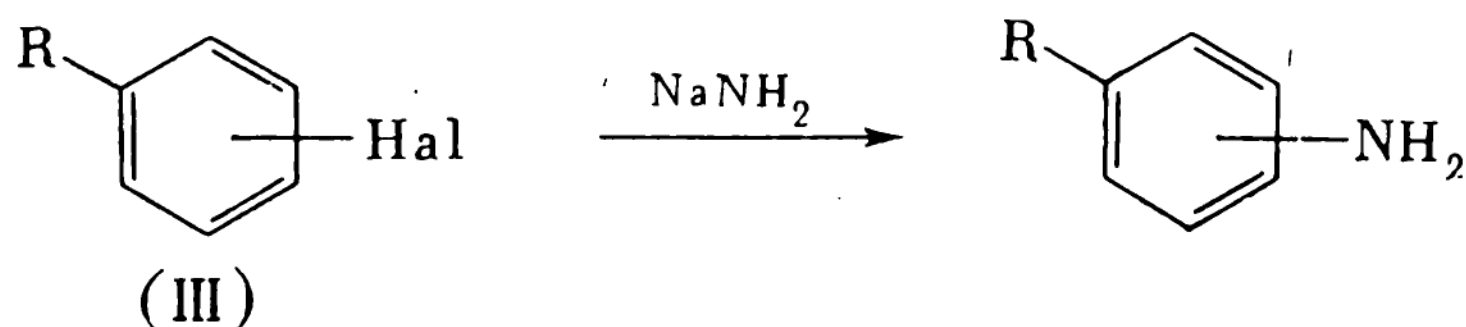


4. NUCLEOPHILIC SUBSTITUTION REACTIONS

59. Arrange the following compounds in order of increasing rate of chlorine substitution:



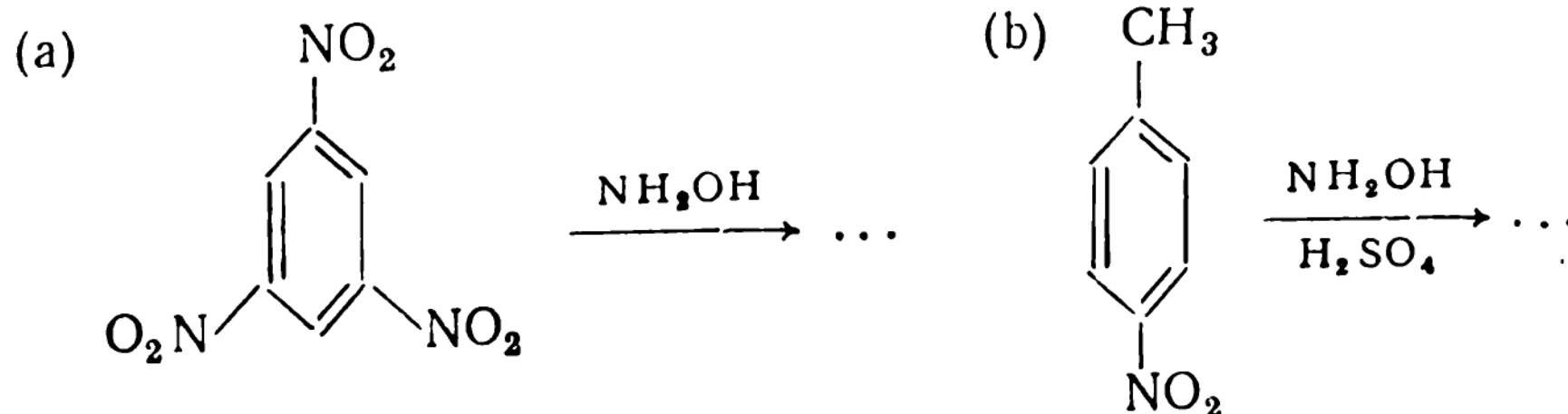
60. It is known that benzene halides of the general formula (III) are converted by the action of sodium amide in liquid ammonia into a mixture of isomeric (*o*- and *m*- or *m*- and *p*-) anilines.

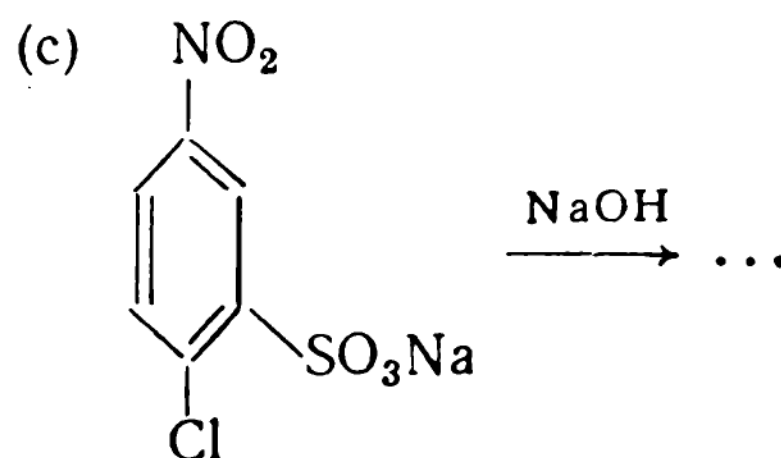


Explain this result and suggest experiments to check up your explanation.

61. How can *N,N*-dialkylanilines be converted into secondary aliphatic amines? Consider the mechanisms of the conversions suggested.

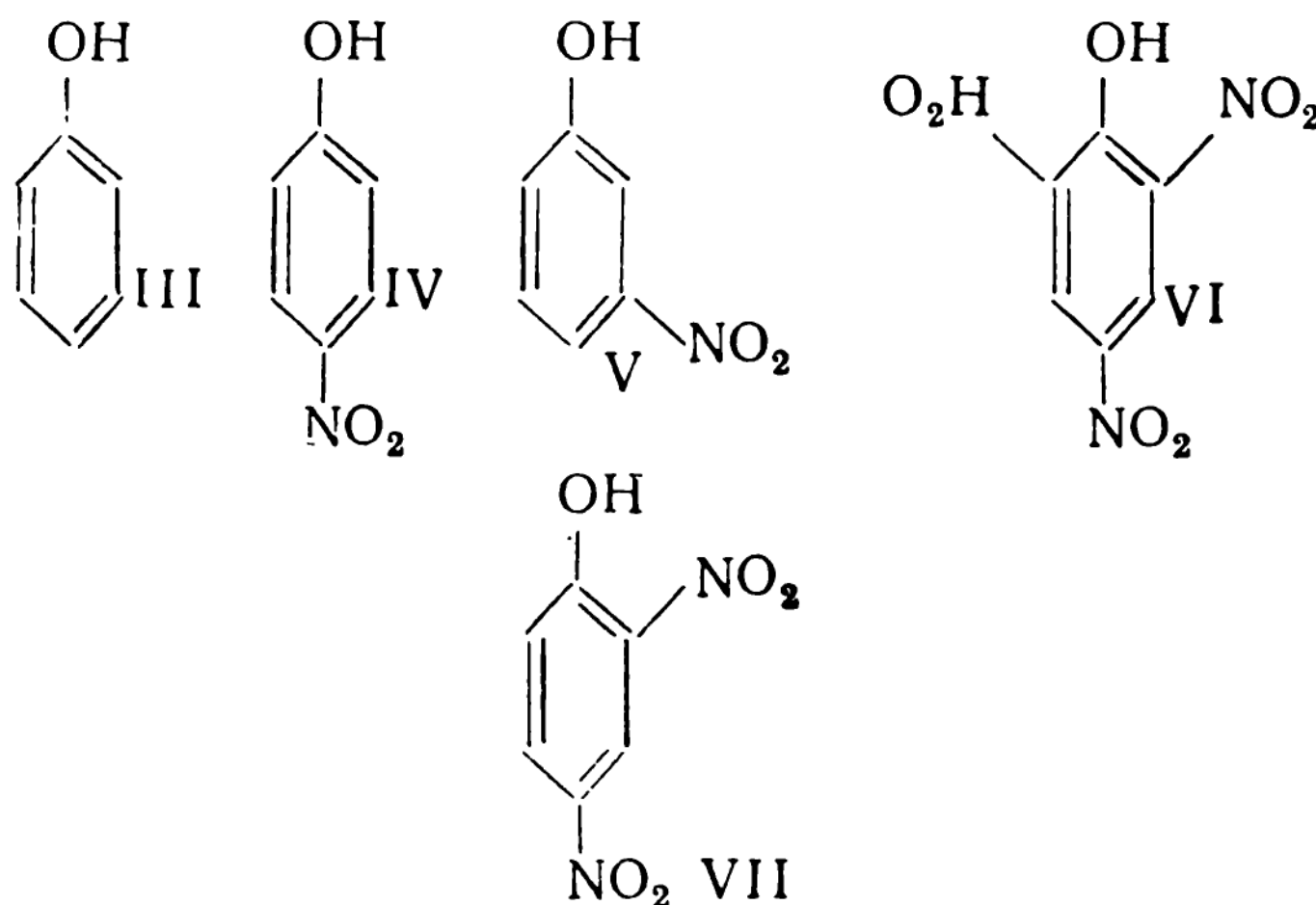
62. Predict the result and discuss the mechanisms of the following reactions:





5. SOME PROPERTIES OF PHENOLS, AROMATIC ACIDS AND AMINES

63*. It is known that phenol and alkylphenols dissolve in caustic alkalis and are insoluble in soda (sodium carbonate). At the same time nitro- and polynitrophenols are capable of dissolving not only in soda but in solutions of sodium bicarbonate as well. Suggest explanations for these facts. Arrange the following compounds in order of increasing acidity:



64*. The values of pK_a for benzoic, salicylic, *p*-hydroxybenzoic and 2,6-dihydroxybenzoic acids are respectively 4.20, 2.98, 4.58, and 1.30. Suggest explanations for this difference in the values of pK_a .

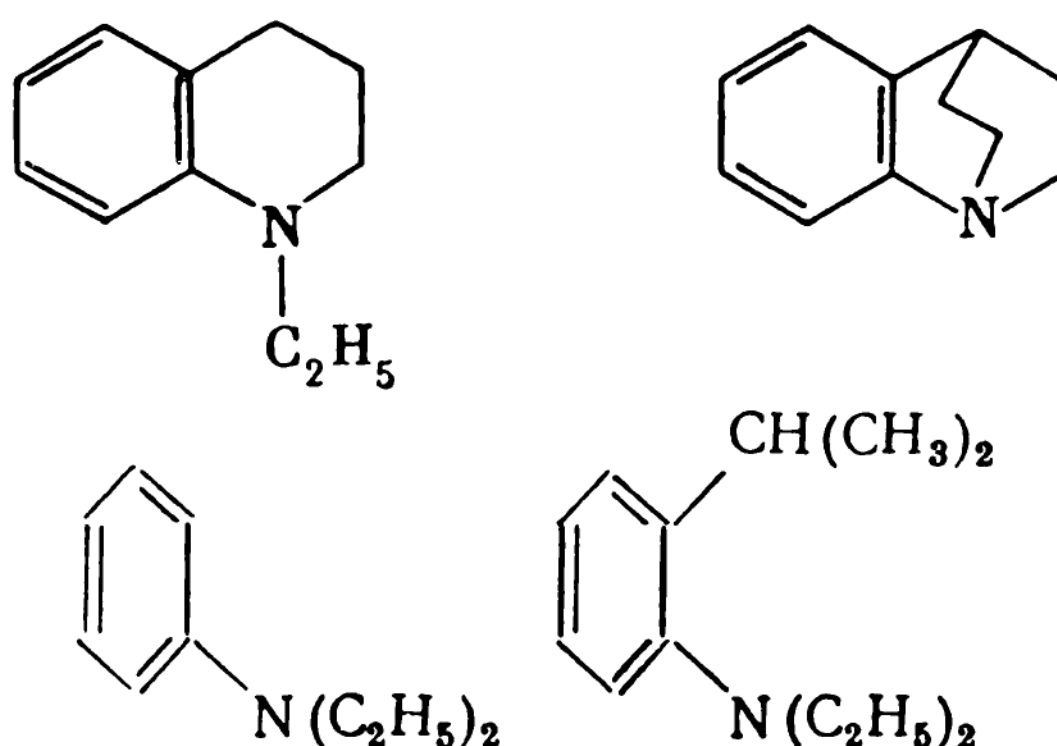
65*. Arrange the following acids in order of increasing acidity: benzoic, *p*-chloro- and *p*-bromobenzoic, *p*-toluic, and *p*-nitro- and *p*-hydroxybenzoic acids.

66. Aniline and cyclohexylamine differ sharply in their pK_b values: 9.38 and 3.32, respectively. Explain this difference.

67. What is the effect of introducing electron-donating and electron-accepting substituents into the benzene ring on the basicity and acidity of phenols? Give examples.

68*. Aniline is a weak base (about two times weaker) than N,N-dimethylaniline. The point of interest is that 2,4,6-trinitroaniline is a much weaker base than N,N-dimethyl-2,4,6-trinitroaniline (about 40,000 times weaker). What is the cause of this difference?

69. Arrange the following compounds in order of increasing basicity:



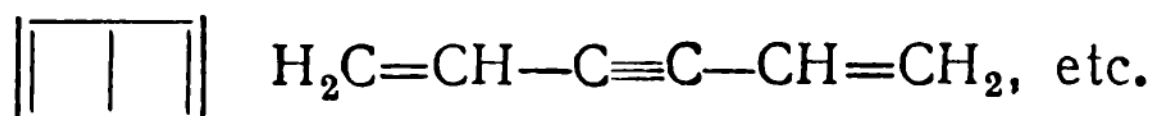
Answers

1. Compounds that are considered aromatic are those the molecule of which is planar and cyclic and contains a conjugated system of multiple bonds consisting of $(4n + 2)$ π -electrons. Besides, at present it is believed that aromatic systems are characterized by the presence of a ring current detected from the spectra of proton magnetic resonance.

All these conditions are satisfied in cases *b*, *f*, *h*, *j*, *m-o*. An interesting example is the compound *p*; though the total number of π -electrons in the molecule is 24 (Hückel's rule is not fulfilled), it should however be kept in mind that only two π -electrons take part in the formation of a conjugated system for each acetylenic bond. The axes of the other two π -orbitals of each acetylene grouping lie in the plane of the molecule and do not for this reason participate in the conjugation. That is why the formation of a conjugated system involves 18 π -electrons ($n = 4$, Hückel's rule is fulfilled). As a result, this compound is more stable than its acyclic analogue and displays a ring current.

Of special interest is ferrocene. Its properties and electronic structure are discussed in A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, vol. 2, J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965, Chapter 14.

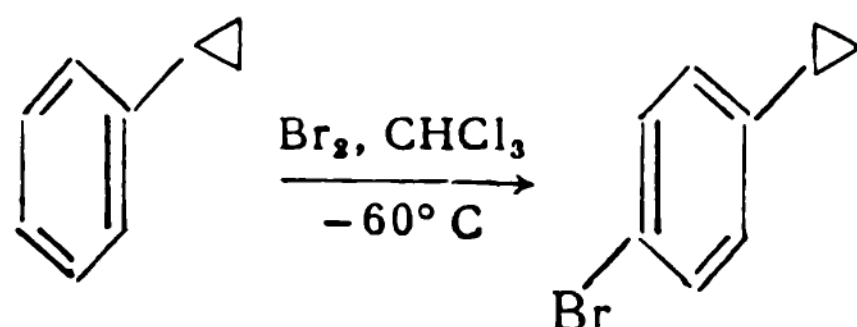
2. A large number of cyclic and linear structures may be suggested for hydrocarbon A. The following may be cited as examples:



Judging by its chemical properties, hydrocarbon B is benzene.

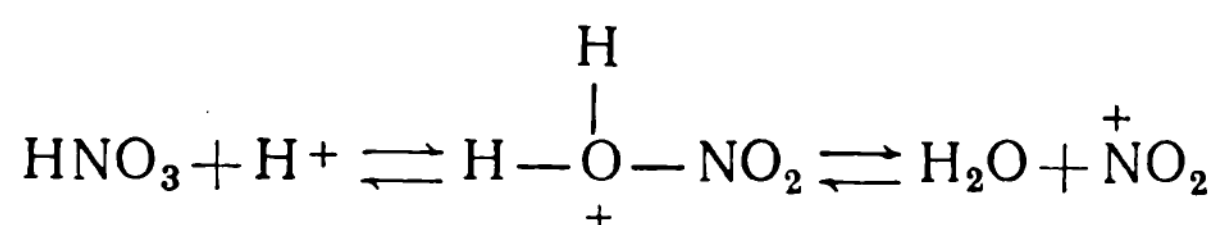
3. Electrophiles are positively charged ions or molecules which contain polar groups. It is evident that the possibility of the occurrence of an electrophilic substitution reaction depends on the specific features of the structure of an aromatic compound as well as on the electrophilicity of the attacking particle. Therefore, in many such reactions, when powerful electrophiles are used, the structure of an arene may be of no deciding importance in estimating the possibility of occurrence of the electrophilic substitution proper. On the other hand, weak electrophilic agents engage in reactions with arenes on condition that either the weak electrophile used is additionally activated (with the aid of protic acids or Lewis acids; examples are the halogenation in the presence of Lewis acids and the alkylation or acylation by the Friedel-Crafts mechanism) or the arene possesses high nucleophilicity (for example, the carboxylation of phenolates by the Kolbe-Schmitt reaction mechanism).

4. (a) For halogenation of aromatic compounds use is often made of Lewis acids, for example, iron, aluminium, zinc, etc., halides. In the case of highly activated aromatic compounds, the halogenation into the nucleus may take place without the use of catalysts. For example, phenylcyclopropane gives a good yield of *p*-bromophenylcyclopropane in neutral solvents by the action of bromine even at -60°C :



It should be noted for comparison that benzene, toluene or isopropylbenzene do not form the corresponding nucleus-brominated products in the absence of the catalysts indicated even at room temperature.

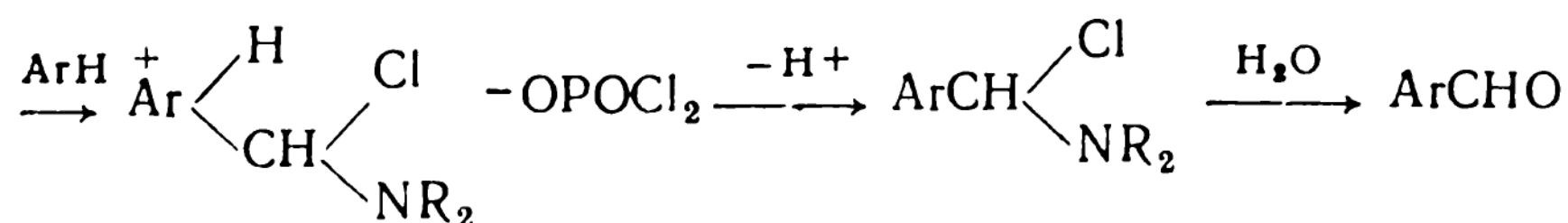
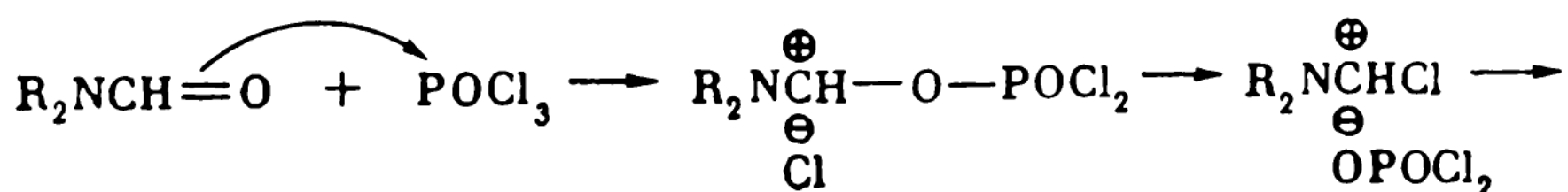
(b) The protonation of a molecule of nitric acid with strong acids (sulphuric, perchloric, and others), the use of nitronium salts (for example, perchlorate or borofluoride), etc.,



(c) It is believed that the electrophilic reagent in the sulphonation reaction is sulphuric anhydride. This is evidenced by the increase of the sulphonation rate with increasing concentration of SO_3 . Moreover, the sulphonation with the aid of D_2SO_4 proceeds more slowly than with the aid of H_2SO_4 . This result is related with the fact that the concentration of DSO_3^+ in D_2SO_4 is higher than that of HSO_3^+ in H_2SO_4 .

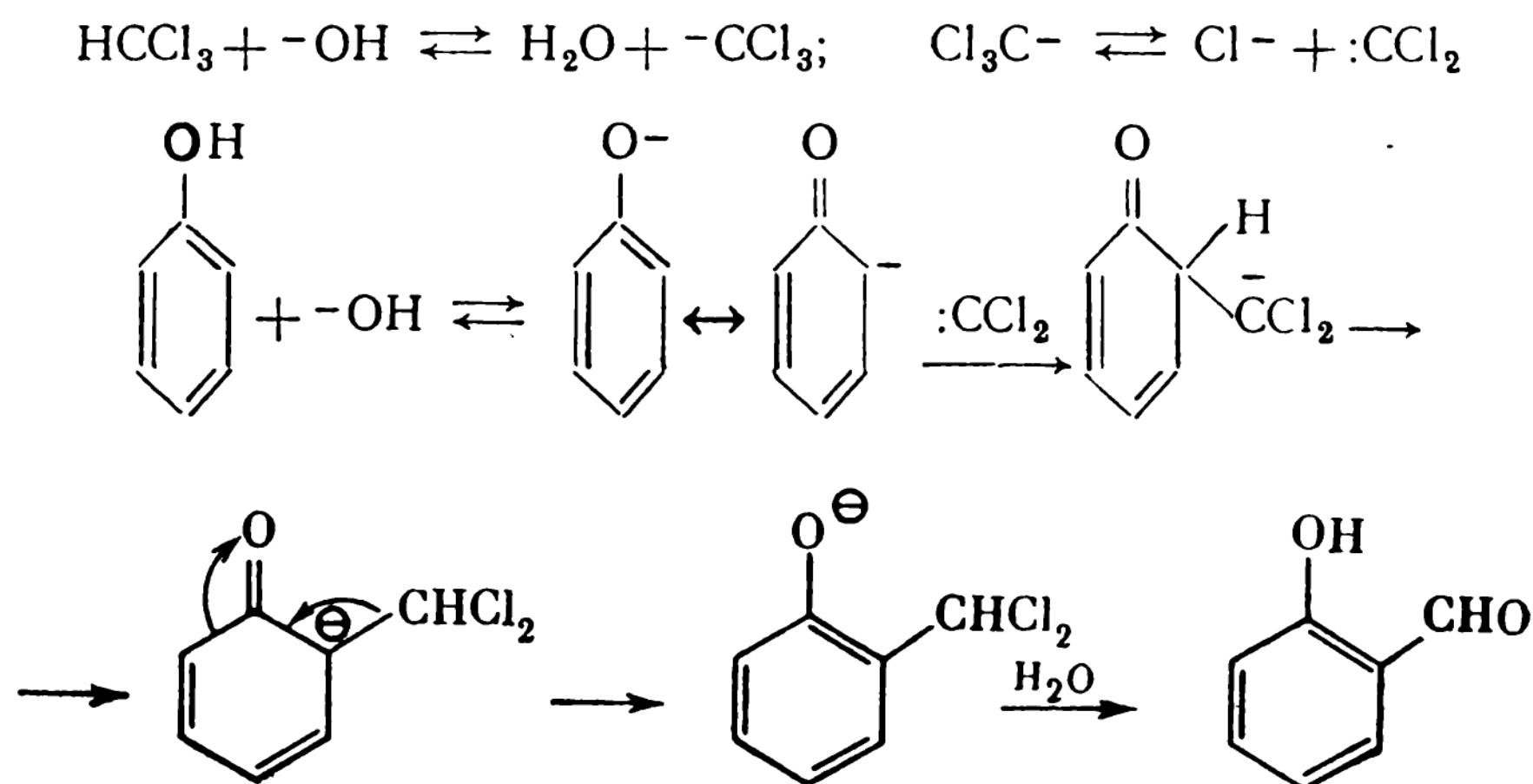
(d) The generation of electrophilic agents in Friedel-Crafts reactions is accomplished with the aid of protic acids (for example, sulphuric or hydrofluoric) and Lewis acids (the halides of aluminium, iron, zinc, gallium, antimony, zirconium, tin, boron, etc.). The mechanism of the alkylation and acylation according to Friedel and Crafts is discussed in detail in the following book: J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965, Chapter 22.

(e) The Vilsmeier reaction is applicable only to activated aromatic compounds (amines, phenols). The formylation of arenes is conducted with the aid of N,N-disubstituted formamides in the presence of phosphorus oxychloride:

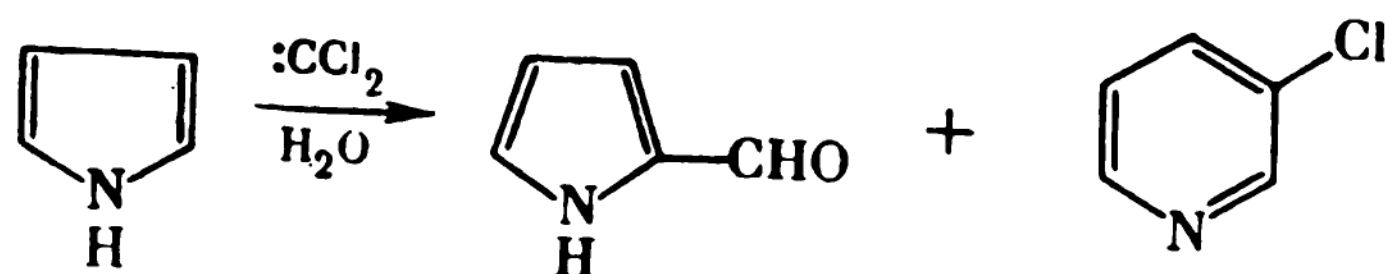


If other acylamides are used in place of formamides, the corresponding aryl ketones may also be obtained.

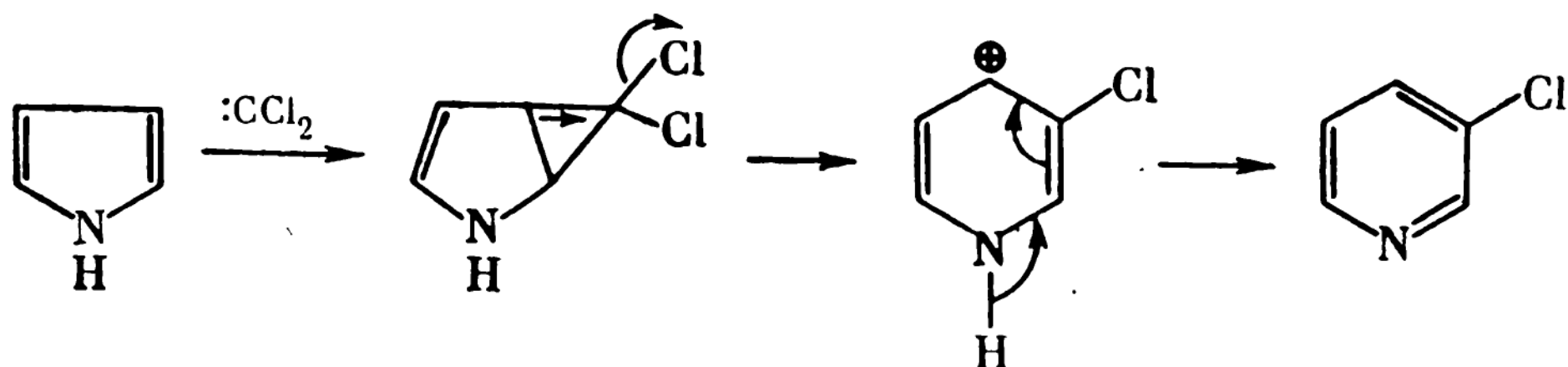
(f) The scheme of formylation by the Reimer-Tiemann mechanism, which is applicable only for phenols and certain heterocyclic compounds of the indole and pyrrole types, involves the generation of dichlorocarbene, which is an electrophilic reagent, from chloroform:



It is interesting that the formylation of pyrrole is accompanied by the partial formation of 3-chloropyridine:



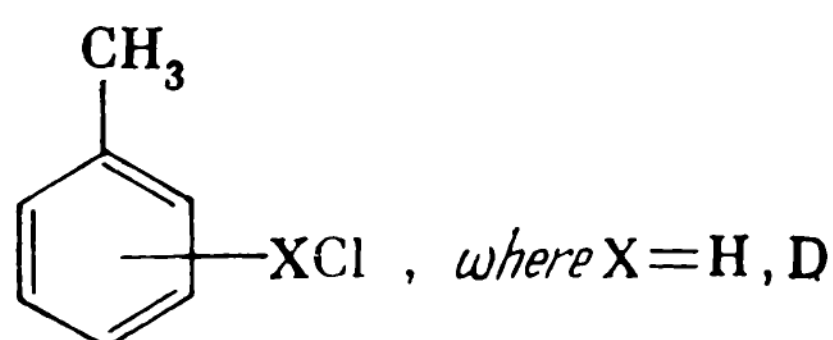
The formation of 3-chloropyridine may be represented by the following scheme:



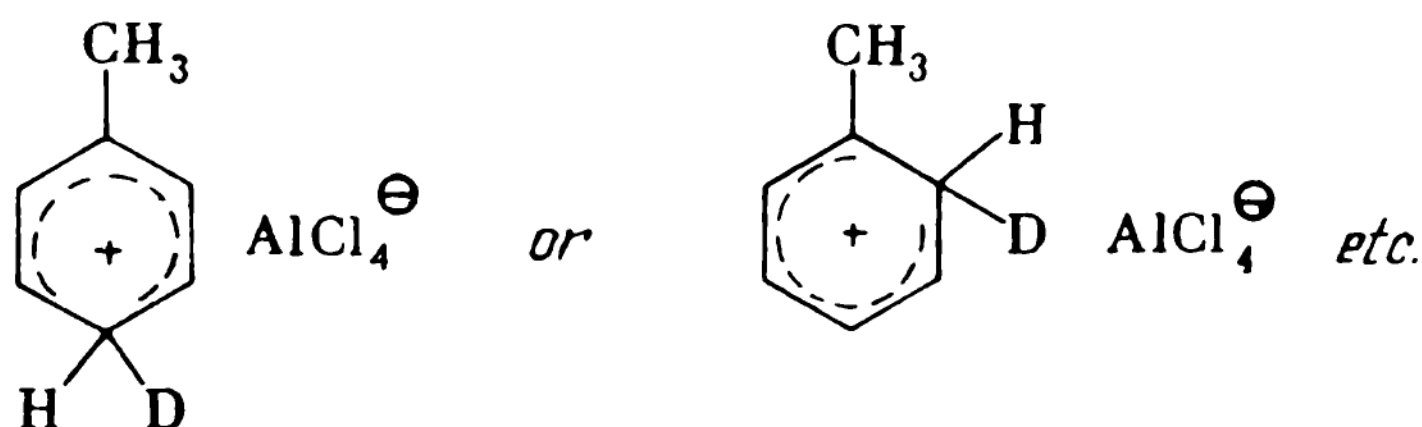
(g) The formylation by the Gattermann mechanism may involve the attack of a complex of the type $\text{ZnCl}_2(\text{HCN})_2 \cdot \text{HCl}$ on an arene (phenols, their esters or heterocyclic compounds),

which results in the formation of the intermediate compound $\text{ArCH}=\text{NH}_2^+\text{Cl}^-$ which after hydrolysis is converted into the corresponding aldehyde.

7. The absence of deuterium exchange in the use of DCl indicates that no carbon-deuterium bond is formed in the toluene-deuterium chloride complex. Therefore, the following structure of the π -complex has been suggested for a colourless crystalline substance:



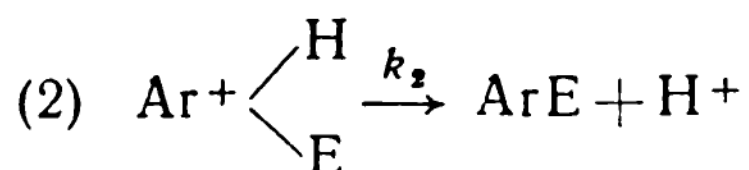
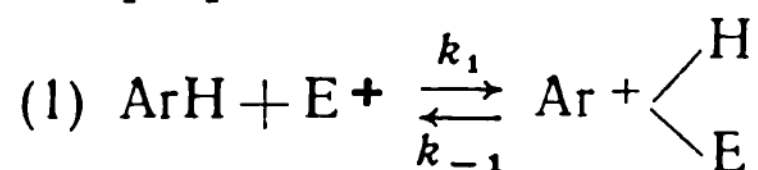
8. The entering of deuterium into the aromatic nucleus of toluene in the presence of Lewis acids (for example, aluminium chloride) is evidence that there is formed, as an intermediate, a σ -complex, in which a carbon-deuterium bond is realized:



9. That the electrophilic substitution of aromatic compounds involves two steps is supported by a large number of experimental data (see, for example, Problems 7 and 8). It is important that for π -complexes the aromatic system is not disturbed, which can be detected by various spectral methods. In its turn, the violation of the aromaticity in the case of σ -complexes is detected with the aid of UV or PMR spectroscopy.

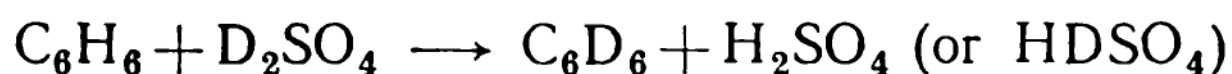
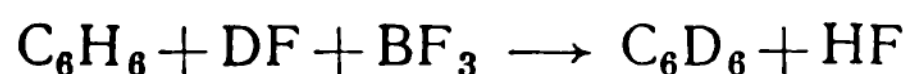
10. If the expulsion of a proton from an aromatic molecule occurred prior to the attack by an electrophilic agent or this attack took place simultaneously with the expulsion of the proton, a considerable isotopic effect must have been observed. In reality it is, as a rule, not great. One of the causes for the occurrence of the isotopic effect may be the

following: according to the general scheme of electrophilic substitution, which may be represented in brief form as a two-step process:



the isotopic effect may appear if k_2 is comparable with k_1 , or is slightly less than k_1 . It should be borne in mind that usually k_1 is smaller than k_2 . Another possibility of the appearance of the isotopic effect may be associated with the following ratio of the rates of each stage: k_{-1} is the same for $\text{Ar}^+ \begin{array}{c} \text{H} \\ \diagup \quad \diagdown \\ \text{E} \end{array}$ and $\text{Ar}^+ \begin{array}{c} \text{D} \\ \diagup \quad \diagdown \\ \text{E} \end{array}$, and $k_2 < k_{-1}$.

12. The following reactions may be cited as examples:



It should be kept in mind that for a sufficiently complete deuterium exchange to be accomplished it is necessary to use a very high excess of deuterium-containing reagents or to carry out deuterium exchange several times, using relatively small amounts of deuterated reagents.

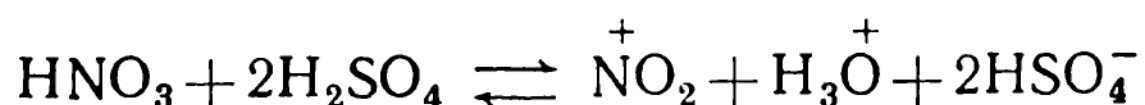
14. The nitration of alkylbenzenes results in the formation of a mixture of *ortho*- and *para*-isomers, containing a small amount of *m*-isomer. The ratio of *o*- and *p*-nitroalkylbenzenes depends, among other factors, on the extent by which the attack of the electrophilic reagent in the *ortho*-position is shielded by the alkyl group. Besides, the amount of *ortho*-isomer depends also on the effective volume of the reagent. On the basis of what has been said it may be expected (and this is what actually occurs) that the nitration of toluene, ethylbenzene, isopropylbenzene and *tert*-butylbenzene under identical conditions will lead to an ever increasing quantity of *p*-isomer and consequently to a decrease in the amount of *o*-isomer. The influence of the effective volume of the reagent on the ratio of *ortho*- and *para*-isomers may be il-

illustrated by the following examples: the nitration of toluene may lead to 56 per cent of *o*-nitrotoluene (and about 40 per cent of *p*-isomer); at the same time, in the sulphonation of toluene the ratio of the products formed is reversed: about 32 per cent of *o*-toluenesulphonic acid and 62 per cent of its *p*-isomer.

It should be taken into account that the steric inhibition of the electrophilic substitution into the *ortho*-position of benzene derivatives is caused only by non-polar (or weakly polar) groups.

15. Depending on the nucleophilicity of the arene and the desired depth of nitration, use is made of a wide range of nitrating agents—from dilute nitric acid (10-60 per cent) to mixtures of concentrated nitric acid and sulphuric acid (concentrated or even with oleum containing 10-20 per cent of free sulphuric anhydride). Apart from mixtures of nitric and sulphuric acids, use is also made of a mixture of the salts of nitric acid with sulphuric acid. Acyl nitrates, nitronium salts (in particular, nitronium borofluoride and perchlorate), nitrogen oxides (N_2O_4 and N_2O_5), a mixture of nitric acid and mercury salts, and others are also used.

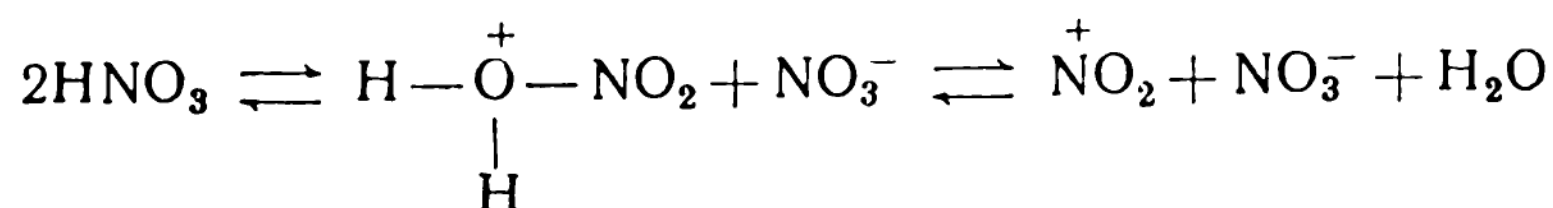
16. (a) It has been found that the decrease of the freezing point of the nitrating mixture is considerably greater (by four times) than might be expected for an ideal solution of nitric acid in sulphuric acid. This result is in accord with the following reaction:



(b) The presence of a nitronium ion in the nitrating mixture or in mixtures of nitric acid with other strong acids has been borne out, in particular, with the aid of the spectra of combination scattering.

(c) The salts of nitronium ion (perchlorate and borofluoride) in neutral solvents (for example, in nitromethane) are powerful nitrating agents.

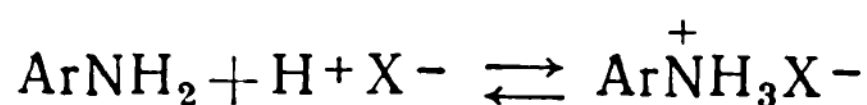
18. The formation of a nitronium ion in concentrated nitric acid takes place according to the following scheme:



Addition of salts of nitric acid causes the equilibrium to be shifted to the formation of undissociated acid molecules. This naturally leads to a decrease in the concentration of the nitronium ion needed for the nitration reaction.

20. The nitration of aromatic compounds is accompanied by oxidizing transformations, replacement of alkyl groups and halogen atoms by nitro groups, dealkylation of phenol ethers, and by oxidation of alkyl groups. It has been shown, for example, that the nitration of benzene leads partly to the formation of dinitrophenol and picric acid. Along with the principal reaction products, from nitrobenzene there is obtained styphnic acid (2,4,6-trinitroresorcinol) and from naphthalene, 2,4-dinitro- α -naphthol.

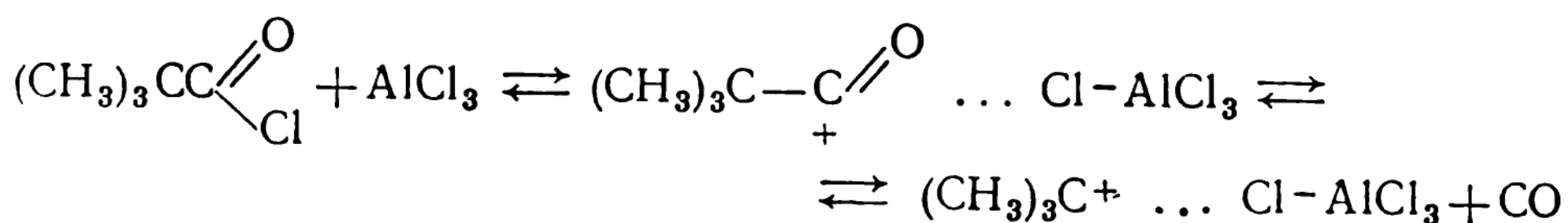
32. When the orienting ability of an amino group (and also of mono- or dialkylamino group) in molecules of aromatic amines is to be assessed, it is necessary to take into account the degree to which the nitrogen atom has been protonated. Aromatic amines, which are comparatively weak bases, form salts capable of dissociating into the initial components:



Another point of importance here is that the protonated and free amines enter into the reaction of electrophilic substitution with different velocities. Cases are therefore possible where even small amounts of a base in equilibrium react much faster than the protonated form, giving only the products of *o*- and *p*-substitution.

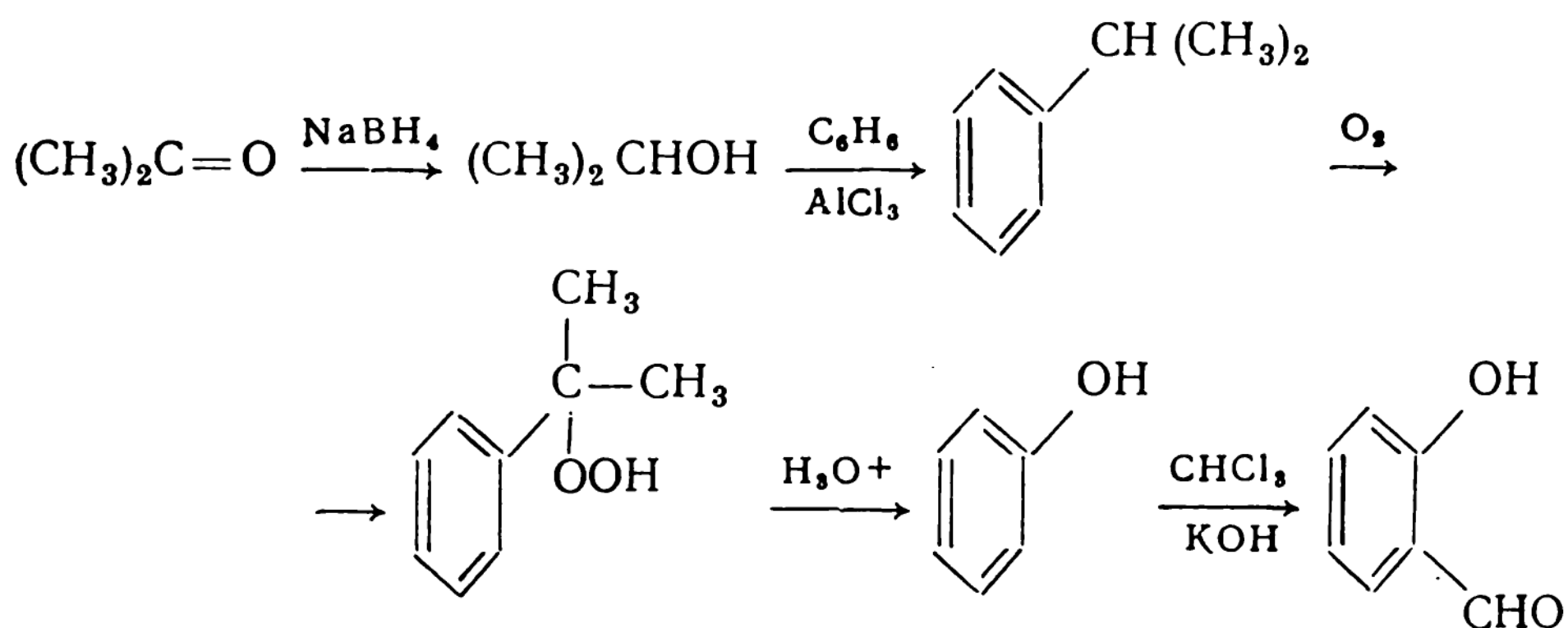
The heating of aniline sulphate causes the dissociation of the salt and the base formed is sulphonated into the *o*- and *p*-positions at a high velocity. In a solution of a concentrated salt of sulphuric acid (the dissociation of the protonated form is suppressed by a large excess of the acid) aniline is sulphonated into the *m*-position.

47. The decarboxylation of trimethylacetyl chloride may be represented by the following scheme:

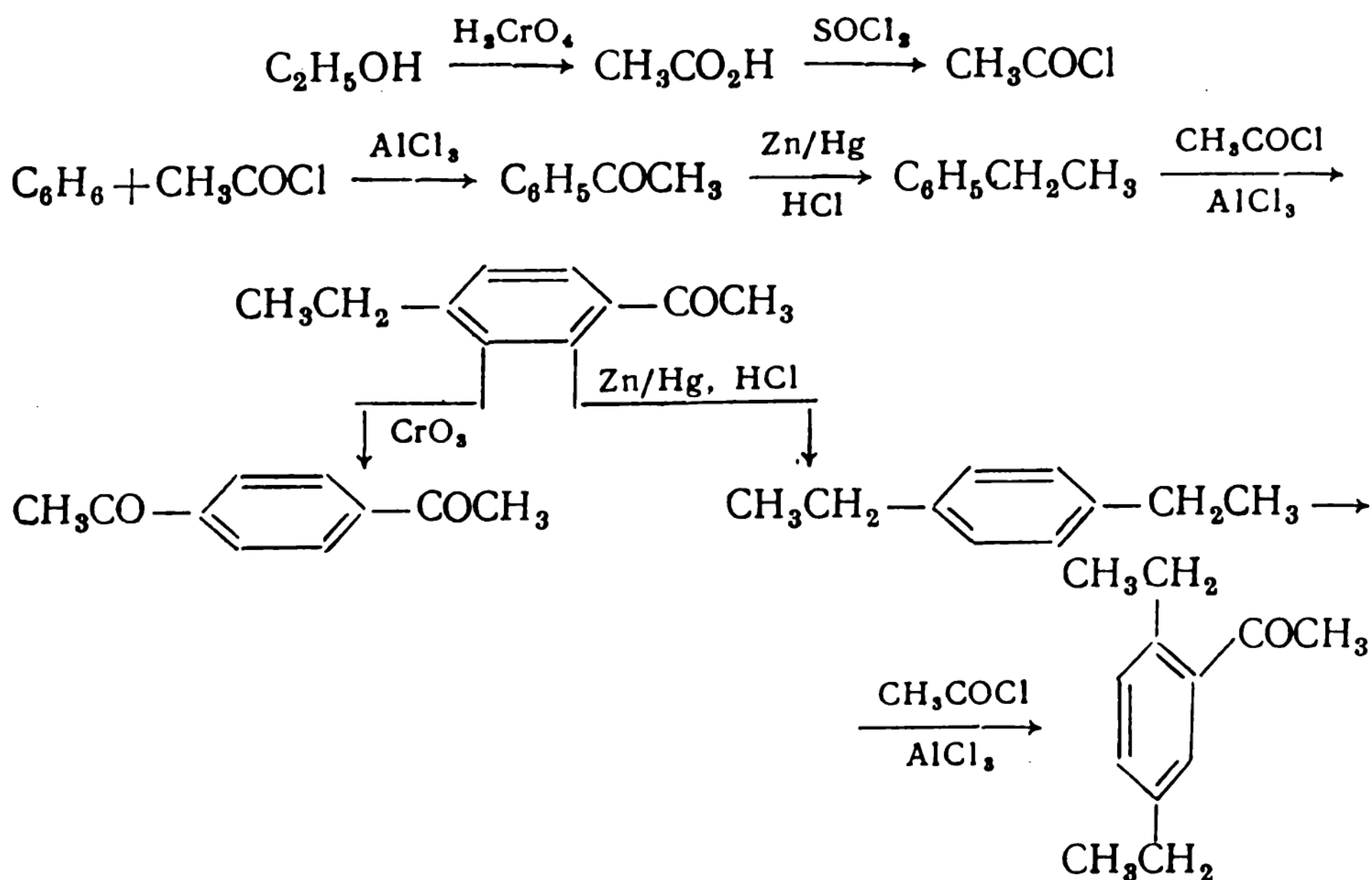


This process proceeds the more completely the lower the probability of interaction of the acid chloride-aluminium chloride complex with a molecule of the aromatic compound. That is why the dilution of the reaction mixture, which lowers the probability of such a reaction, contributes to the formation of alkylated, and not acylated, products.

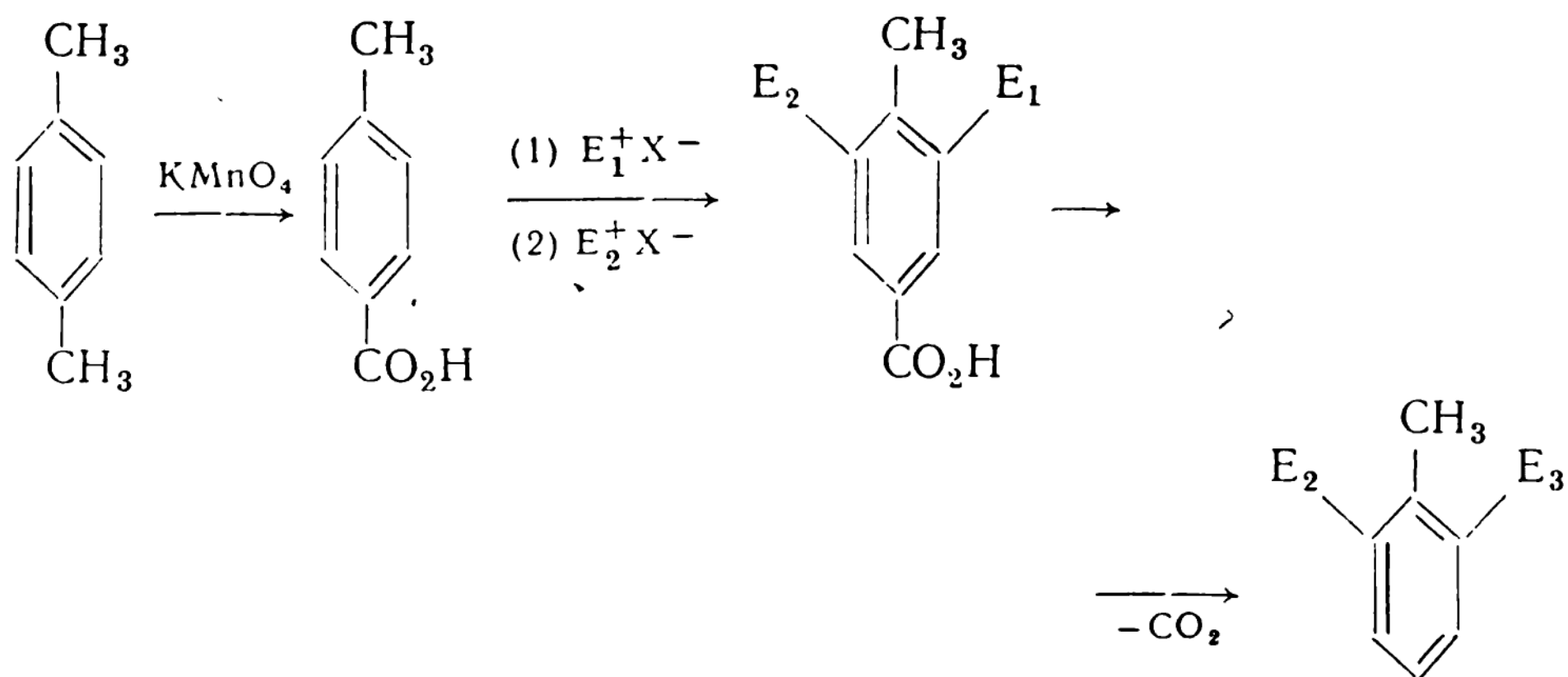
52. One of the possible schemes for preparing salicylic aldehyde is the following:



53. To prepare *p*-diacetylbenzene and 2,5-diethylacetophenone the following routes may be used:



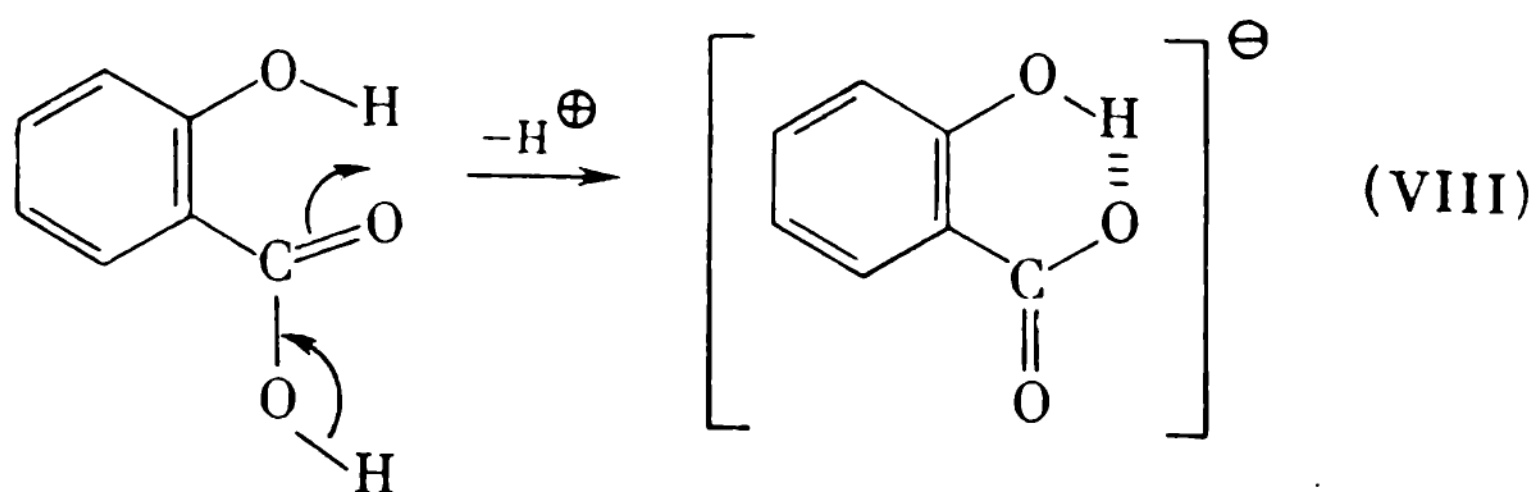
55. 2,6-Disubstituted toluenes can be prepared from *p*-xylene according to the following general scheme:



where E_1^+ and E_2^+ are the corresponding electrophilic agents.

63. The increase of the acidity of phenols resulting from the introduction of electron-accepting substituents into the aromatic ring is very sharp in the case of nitro and poly-nitro compounds. Indeed, the pK_a of phenol (III) is 9.9; of *p*-nitrophenol (IV), 7.14; of 2,4-dinitrophenol (VII), 4.01, and that of picric acid, (VI), 1.02. This increase of acidity for compounds (IV), (VII), and (VI) is ascribed to the presence of the inductive and resonance effects of the nitro group. In the case of *m*-nitrophenol (V) ($\text{pK}_a = 8.35$) an increase in acidity takes place by the inductive mechanism alone.

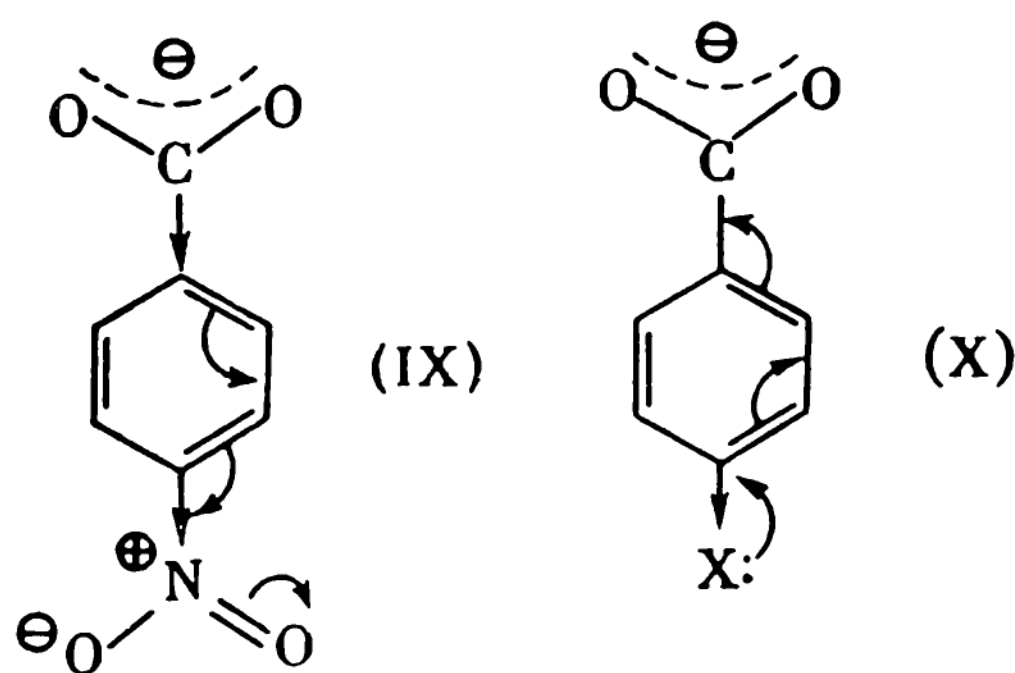
64. For the pK_a value of benzoic and *p*-hydroxybenzoic acids see Problem 65. To account for the sharp increase of the acidity of the other two acids one must consider the molecule of salicylic acid: the intramolecular hydrogen bond stabilizes the resulting anion (VIII):



Such stabilization is still more pronounced in the presence of one more *o*-hydroxyl group (in the molecule of 2,6-dihydroxybenzoic acid).

This explanation is supported by the fact that *o*-methoxybenzoic acid (the formation of a hydrogen bond of the type indicated is impossible in the molecule of this compound) is much weaker ($pK_a = 4.09$).

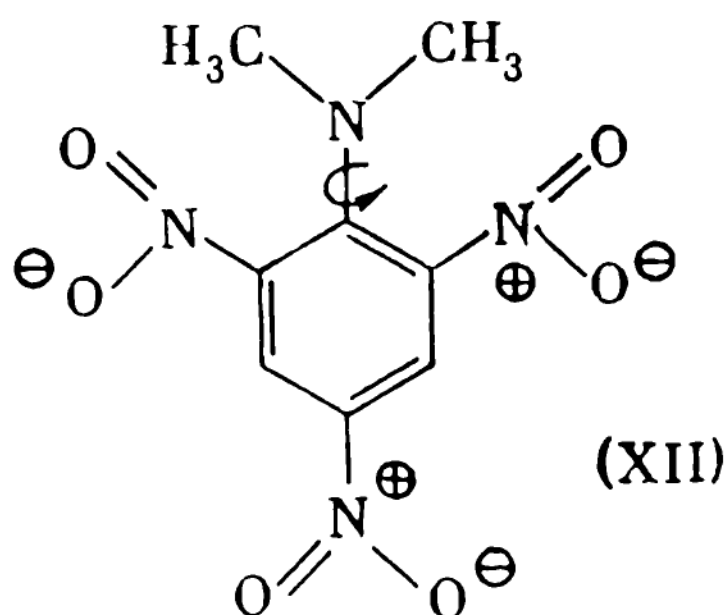
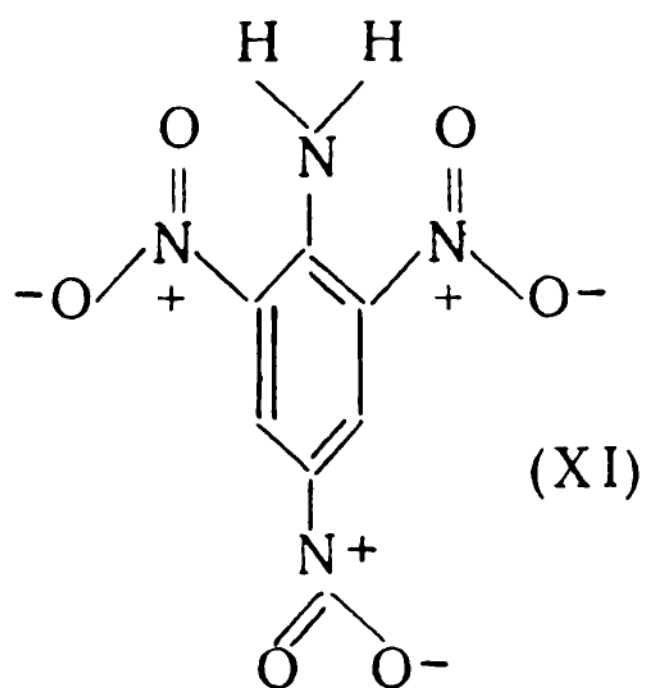
65. As compared with benzoic acid ($pK_a = 4.20$), *p*-toluic acid exhibits a low acidity ($pK_a = 4.34$) because of the positive inductive effect of the methyl group. *p*-Chloro-, *p*-bromo-, and *p*-nitrobenzoic acids are substantially more acidic; this particularly refers to *p*-nitrobenzoic acid ($pK_a = 3.43$). This is caused by the considerable negative inductive effects of all the substituents indicated, and in the case of the nitro group, by the negative mesomeric effect as well. The last circumstance leads to the stabilization of the carboxylate ion (IX) resulting from dissociation. As to *p*-chloro- and *p*-bromobenzoic acids (their pK_a values are respectively 3.99 and 4.00) the positive mesomeric effect of the substituent partly compensates for the negative inductive effect [see formula (X)] and, as a result, the acidity of the carboxylic group is only slightly increased.



Of special interest is *p*-hydroxybenzoic acid, whose pK_a is equal to 4.58. This fact should be treated from the viewpoint of a more sharply pronounced (predominating) positive mesomeric effect of the hydroxyl group.

68. That aniline and dimethylaniline differ but slightly in basicity is in accord with the conceptions of the small positive inductive effect of methyl groups (dimethylaniline is a somewhat stronger base than aniline).

To account for the sharp difference in the basicities of 2,4,6-trinitroaniline and 2,4,6-trinitrodimethylaniline it is necessary to consider their molecular models [see structures (XI) and (XII)].



In the case of 2,4,6-trinitroaniline the basicity of the amino group is considerably decreased due to the conjugation of the electron pair on the nitrogen atom with the aromatic nucleus. The increase of the volume of the substituents at the nitrogen atom (methyl groups instead of hydrogen atoms in N,N-dimethyl-2,4,6-trinitroaniline) causes the rotation about the C—N bond indicated in formula (XII), which leads to a reduction of the overlap of the *p*-electrons of the nitrogen with the π -electronic aromatic system and hence to an increase of the basicity of the amine (XII).

CHAPTER 8

AROMATIC AMINES AND DIAZONIUM COMPOUNDS

Amines of the aromatic series derived mostly by reduction of the corresponding nitro compounds are widely employed in the synthesis of intermediate products, dyes, medicines, and many other preparations.

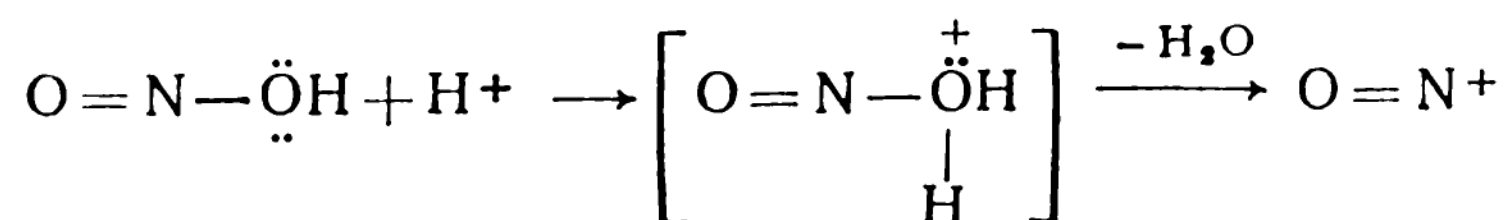
One of the most important ways of using aromatic amines is the preparation of diazo, or diazonium, compounds which, owing to their high reactivity and to the practical significance of their conversion products, play an important role as an individual class of organic compounds. That is why the process used for preparing diazo compounds—the so-called *diazotization reaction*—has found wide application both in industry and in the laboratory.

The present chapter covers problems and exercises in methods of preparing, and in the properties of aromatic amines and diazonium compounds, in their use for organic synthesis and production of azo dyes.

Diazo compounds result from the interaction of primary aromatic amines with nitrous acid.

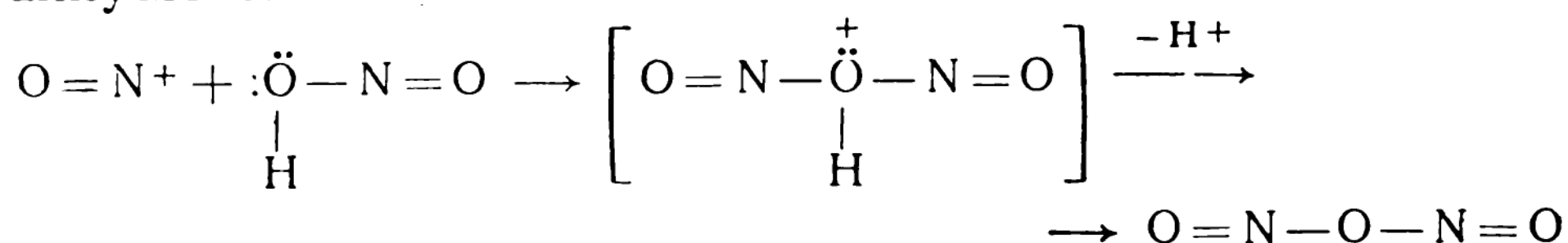
The reactions of aliphatic and aromatic primary and secondary amines with nitrous acid have much in common with respect to mechanism.

Since the reaction is conducted in the presence of a mineral acid, the interaction is supposed to start with the protonation of the hydroxyl oxygen of nitrous acid and the formation of the nitrosonium ion:



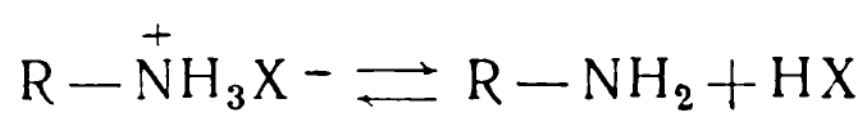
The nitrosonium ion reacts with the oxygen of the hydroxyl group of another molecule of nitrous acid to give nitrous

anhydride:

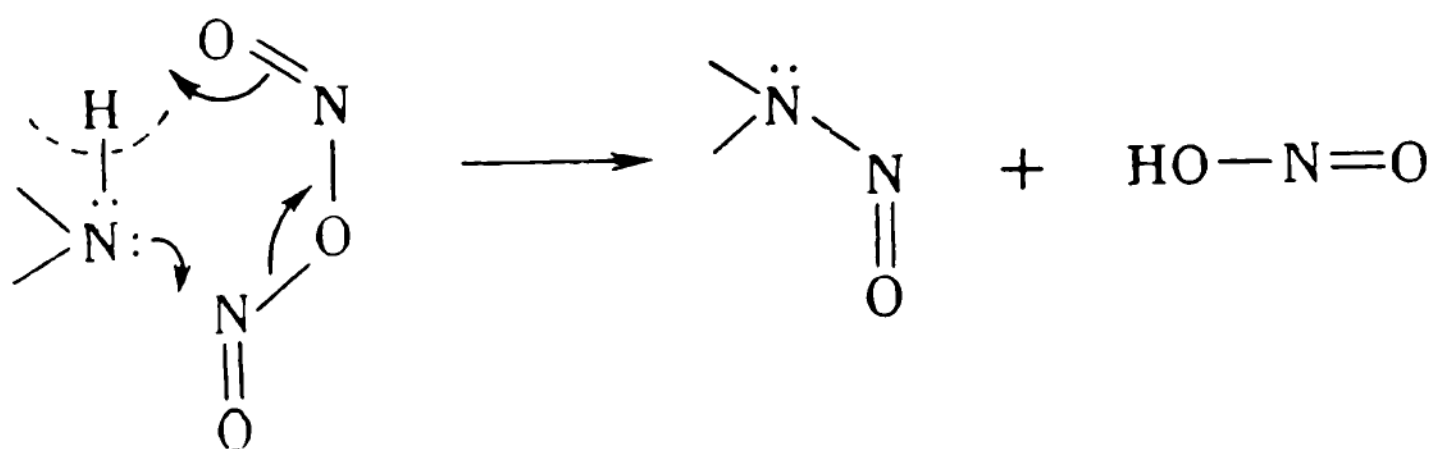


The nitrogen atoms of nitrous anhydride are already much more deficient in electron density than those of the starting nitrous acid.

It has been proved that a free amine, and not its salt, reacts with the nitrosating agent; evidently, there is an equilibrium:

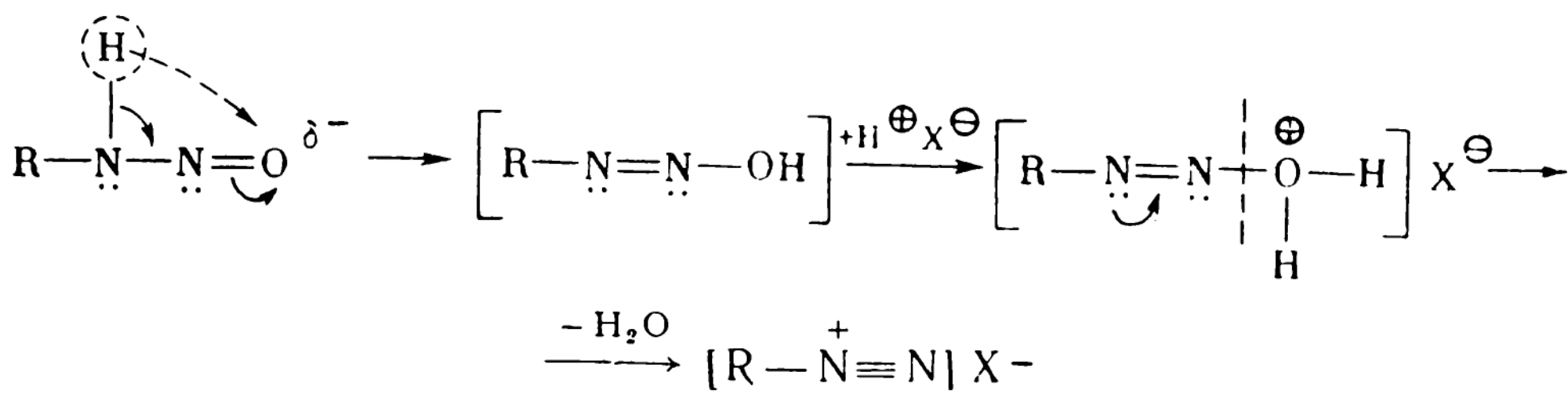


Nitrous anhydride serves in the reaction as a bifunctional reagent, which not only attacks as an electrophile the nitrogen of the amino group but also accepts the proton splitting off as a result of the reaction; therefore there are grounds to suppose that the reaction involves a six-membered transition state:

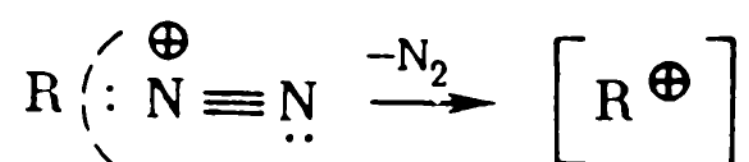


This stage resulting in the formation of nitroso amines is the last one for the secondary amines participating in the reaction.

The nitroso amines obtained from primary amines however undergo further conversions:



The fate of the diazonium cation formed depends on the nature of R. Where R is an aliphatic radical there takes place the liberation of a nitrogen molecule



and the resulting carbonium ion reacts preferably with water to form an alcohol (the reaction is usually conducted in aqueous solution). In those cases where R is an aromatic radical the reaction can be stopped at low temperatures at the stage of formation of a diazonium salt.

In contrast to aliphatic diazonium salts, the salts of aryl diazonium are relatively stable and usually decompose with the evolution of nitrogen only at temperatures above 0°C.

The group $-\overset{+}{N} \equiv N$ in these compounds is more strongly bound with the carbon of the benzene ring and is less liable to evolve as molecular nitrogen. The more pronounced the electron-accepting properties of the aryl radical the more stable is the corresponding diazonium salt.

When the diazo group is displaced by other groups or atoms, the linkage of nitrogen with the carbon atom of the benzene ring may be ruptured both heterolytically (A) and homolytically (B):



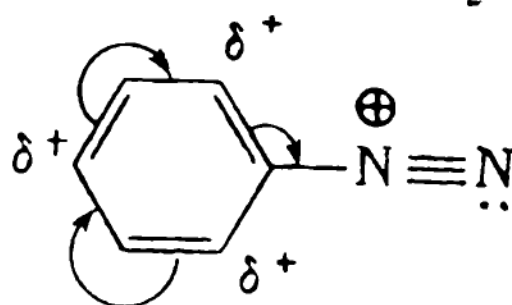
with the formation of either a phenyl cation or a phenyl radical, respectively.

The intermediate formation of these extremely reactive species can be proved only indirectly, by carrying out the reaction in the presence of certain substances and isolating the reaction products formed as by-products. The heterolytic rupture of the C—N bond usually takes place in the thermal decomposition of diazonium salts and the homolytic one, in the presence of the salts of univalent copper or powdered metallic copper, which are electron-donors.

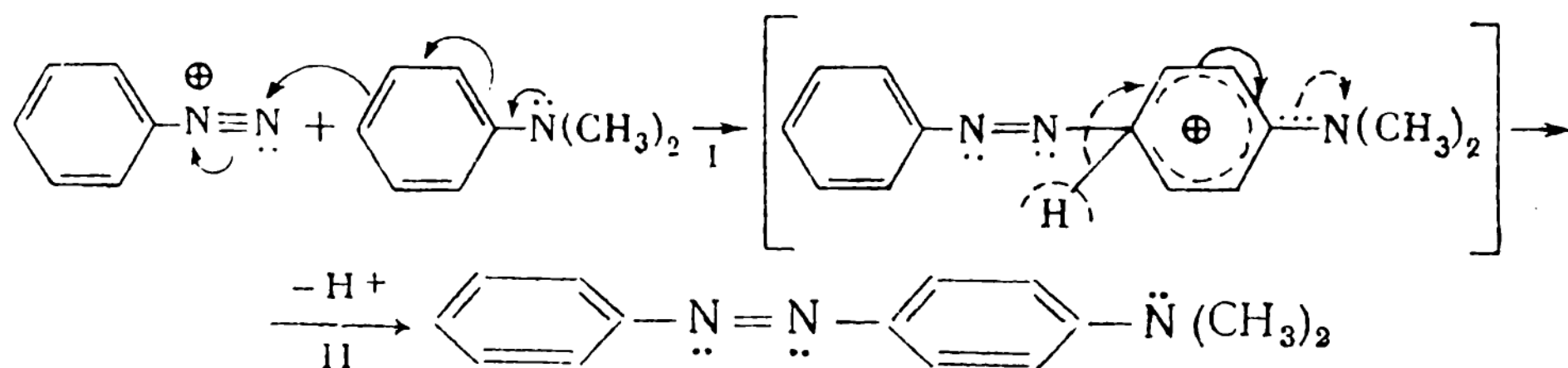
The *azo coupling* reaction, as has been established at present, is a typical electrophilic substitution reaction in the

aromatic nucleus, the diazonium cation playing the role of an electrophilic particle.

The electrophilic strength of the diazonium ion is not great as compared with at least the nitronium ion since because of the +M effect of the phenyl the positive charge that it carries is found to be spread, apart from the nitrogen, over the *ortho*- and *para*-positions of the benzene ring:



Phenyldiazonium ion can therefore react only with such compounds in which the nucleus is highly enriched with electrons, say, with dialkylaniline; even anisole appears to be incapable of entering into an azo coupling reaction with phenyldiazonium (the methoxy group is appreciably inferior as an electron-donor to the dialkylamino group). The reaction proceeds in two stages via the formation of a σ -complex:



Since the first stage is relatively slow, there is observed during the reaction an isotopic effect, i.e., the deuterated dimethylaniline reacts at a much (approximately by 5-8 times) lower velocity.

Problems and Exercises

1. REDUCTION OF THE NITRO GROUP ATTACHED TO THE AROMATIC NUCLEUS

1. What compounds are formed in the reduction of nitrobenzene in an alkaline medium? Specify the reduction conditions under which each of them can be obtained. Write the equations of the reactions.

2. Name the reduction products of nitrobenzene in an acidic medium. Indicate the reducing agent used and the method of reduction.

3. Enumerate the methods of preparing nitrobenzene.

4. What reducing agent is used to prepare phenylhydroxylamine from nitrobenzene?

5. Why can phenylhydroxylamine be obtained only in solutions close to neutral?

6*. What compounds are formed by the action of concentrated sulphuric and hydrochloric acids on phenylhydroxylamine and *p*-tolylhydroxylamine? Discuss the mechanism of the reactions.

7. How does nitrobenzene react with phenylhydroxylamine in a medium close to neutral? Consider the mechanism of the interaction.

8*. Write the equation of the reaction between phenylhydroxylamine and benzaldehyde.

9. Prepare from nitrobenzene the ammonium salt of N-nitrosophenylhydroxylamine (an analytical reagent called cupferron).

10. Name at least five methods of reducing nitrobenzene to aniline (using various reducing agents). Set up equations for the corresponding reactions.

11. What does partial reduction mean? Give examples of using this reaction for preparative purposes.

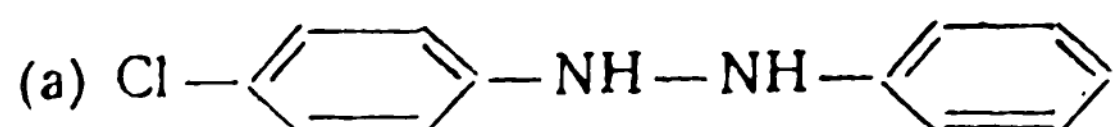
12*. Using benzene and inorganic reagents, prepare all the isomeric aminophenols.

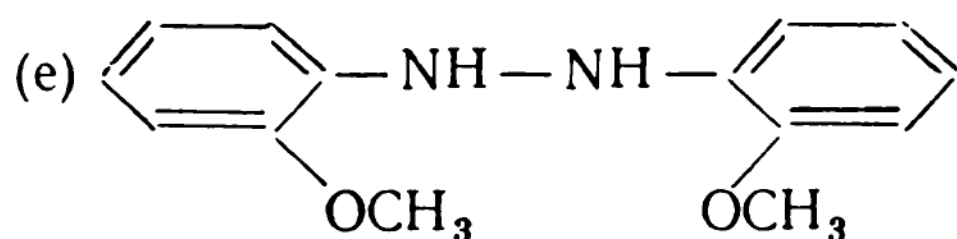
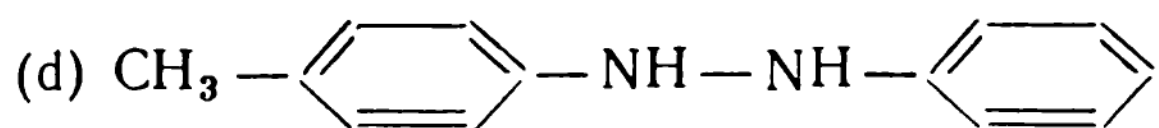
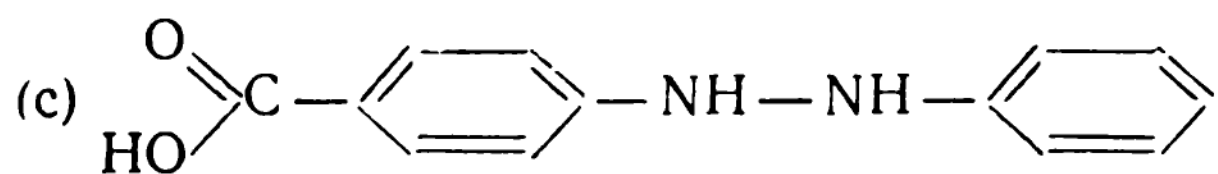
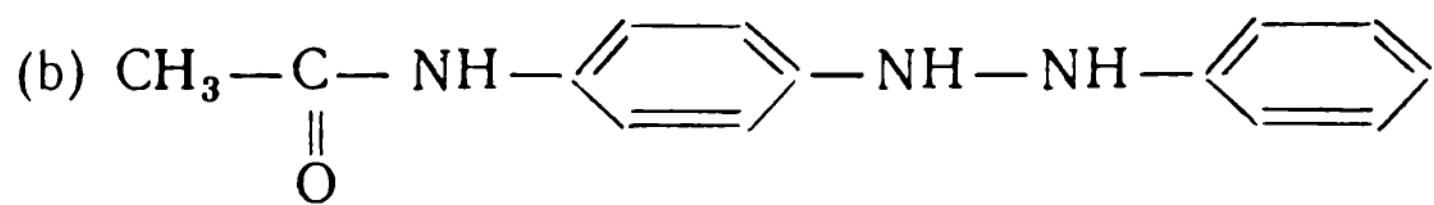
13. How could you account for the fact that the reduction of nitrobenzene with zinc (or stannous chloride) and concentrated hydrochloric acid gives, in addition to aniline, *p*-chloroaniline?

14*. What do you know about the mechanism of the benzidine rearrangement?

15. What conversions are known to be called the diphenyl-line and semidine rearrangements?

16*. What conversions will be brought about by the action of sulphuric acid on the following substituted hydrazobenzenes:





Write all possible reaction products.

17. What conversions are called the *ortho*- and *para*-semi-dine rearrangements? Give concrete examples.

18*. What compounds result from the benzidine rearrangement of tetraphenylhydrazine?

19*. Give the names of at least three methods of preparing azoxybenzene. Set up the equations of the reactions.

20. What is the spatial structure of the stable isomer of azobenzene if it is known that its dipole moment is equal to zero?

21*. How could you account for the fact that the C—N bond in the *trans*-isomer of azobenzene is shorter (1.41 Å) than that in the *cis*-isomer (1.47 Å)?

22. Discuss the advantages and limitations of the methods of reduction of nitrobenzene to aniline in acidic, neutral, and alkaline solutions.

23*. An ever increasing use has recently been made of the method of reducing aromatic nitro compounds with hydrazine hydrate in the presence of a skeleton nickel catalyst (Raney nickel). What are the advantages and the field of application of this method?

24*. Using phenol and inorganic reagents, prepare picramic acid (2,4-dinitro-6-aminophenol).

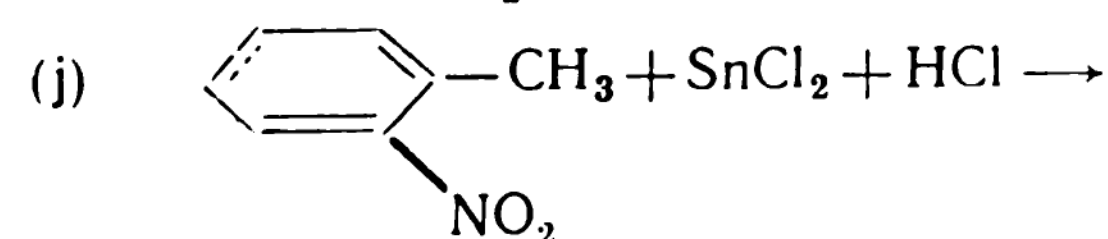
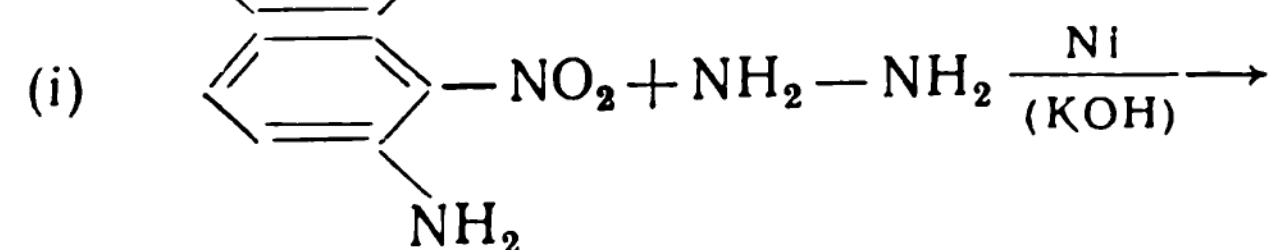
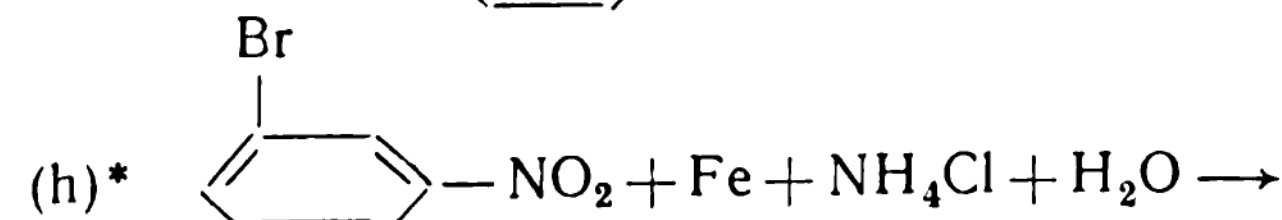
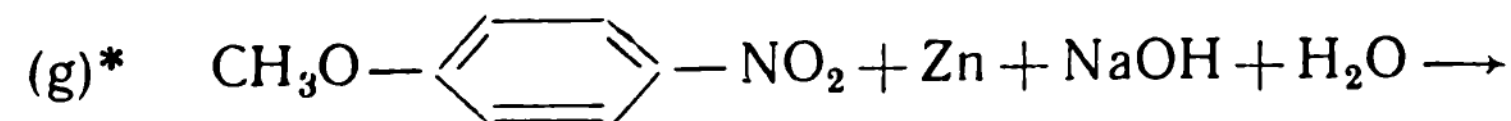
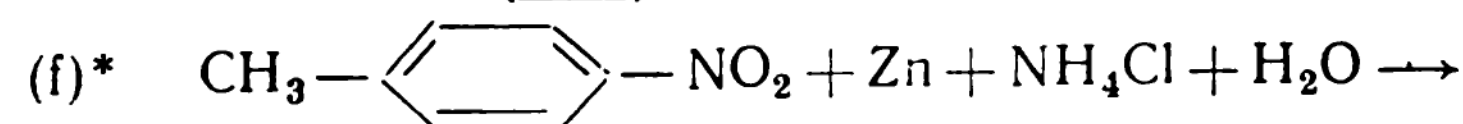
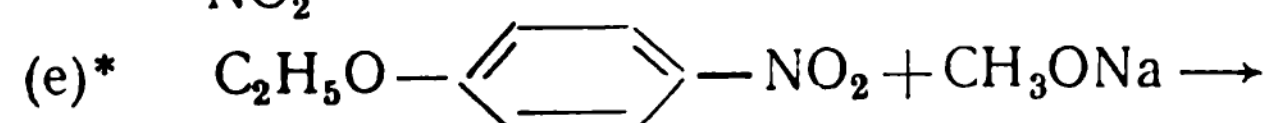
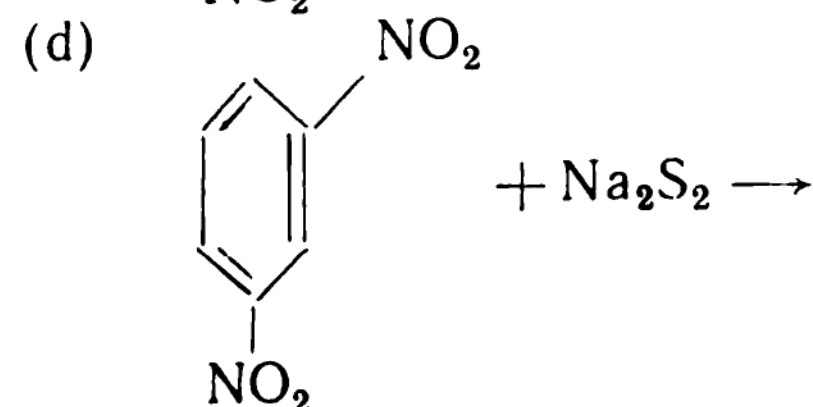
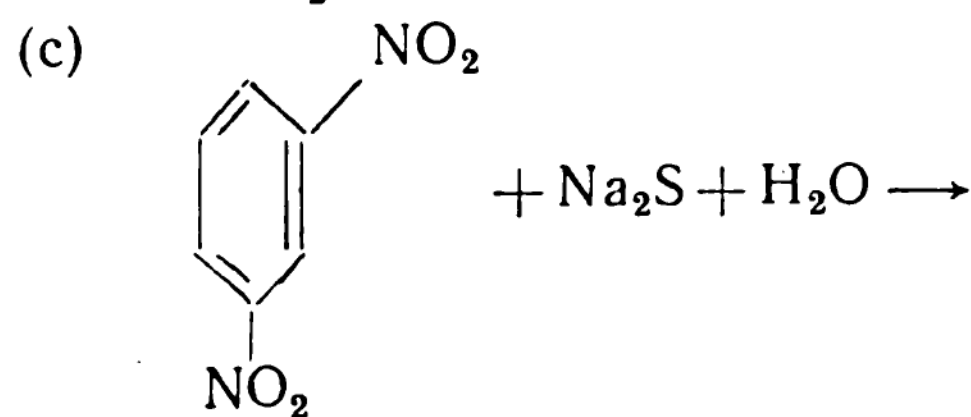
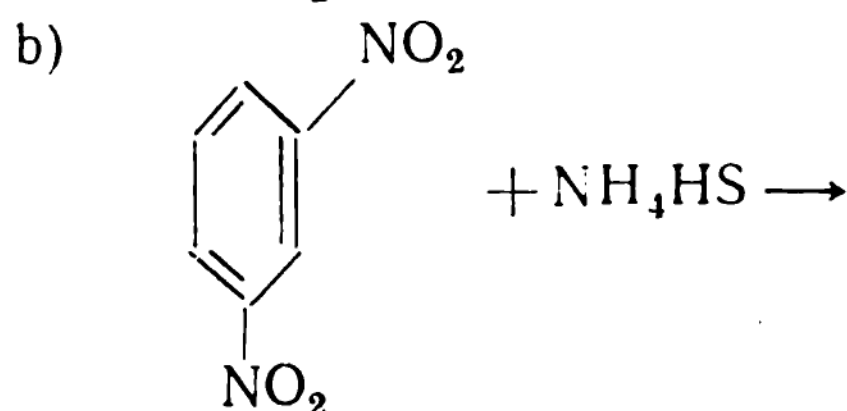
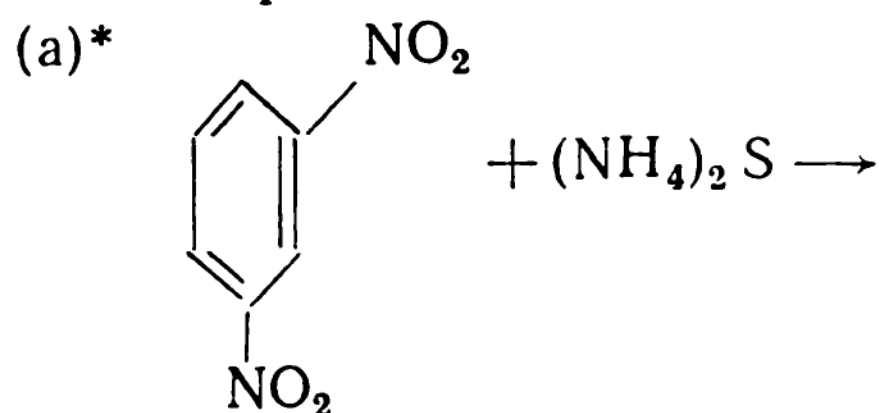
25. Prepare N-methyl-*p*-phenylenediamine from N-methylaniline and inorganic reagents.

26*. Prepare *p*-aminophenol from nitrobenzene by a two-step synthesis.

27. Prepare all the isomeric nitroanilines and anizidines from benzene and inorganic reagents.

28. Prepare *m*-bromoaniline and 2,4-diaminoanisole from benzene and inorganic reagents.

29. Complete and balance the following equations:



2. PREPARATION OF DIAZO COMPOUNDS

30. Outline the mechanism of the reaction of primary and secondary aromatic and aliphatic amines with nitrous acid.

31. Why is the diazotization reaction ordinarily conducted at a low temperature?

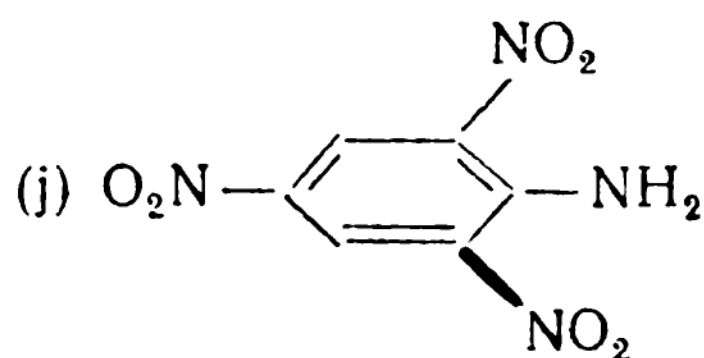
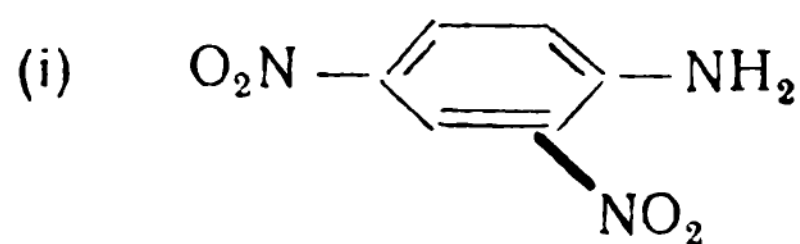
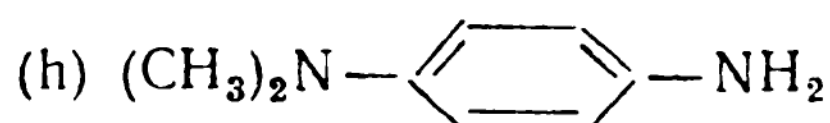
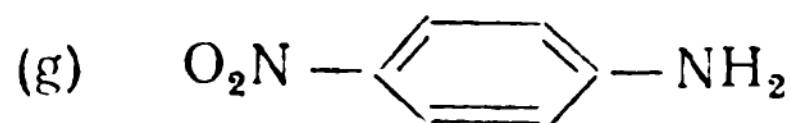
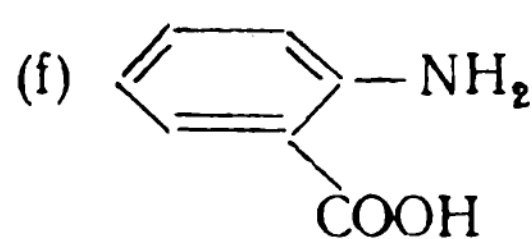
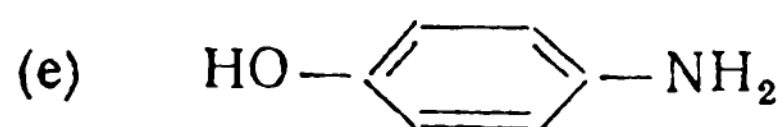
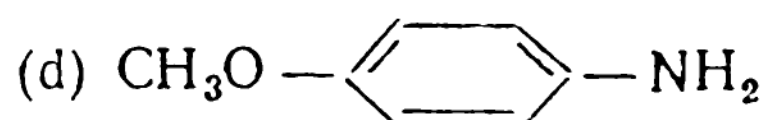
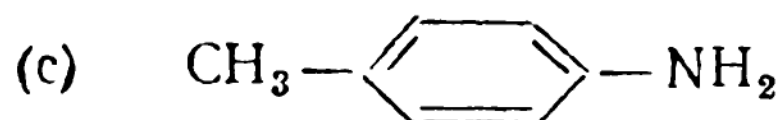
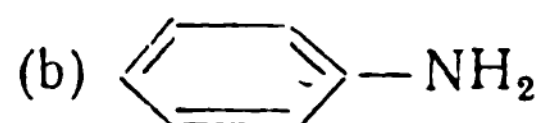
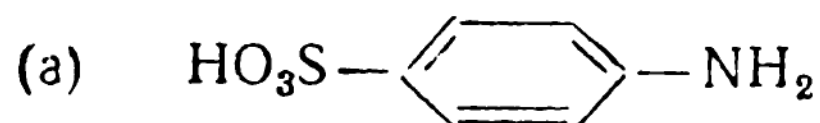
32. What will happen with a diazo compound if its solution is allowed to stand at room temperature for several hours?

33*. What difficulties arise in the diazotization of *ortho*-, *meta*-, and *para*-phenylenediamines? How are bis-azo dyes corresponding to bis-diazo compounds produced in practice from phenylenediamines?

34. Identify the precipitate that separates occasionally during the diazotization of *p*-nitroaniline. How can its formation be prevented?

35*. What is "direct" diazotization and what "reverse"? In what cases are these methods used?

36*. Suggest a method of diazotization for each of the following aromatic amines:



What conversions will the corresponding diazonium salts undergo when attacked by an alkali?

37. Why is an excess of mineral acid required for a diazotization reaction to be carried out?

38*. How is the end of a diazotization reaction recognized? How can excess nitrous acid be removed from the reaction mixture after the diazotization reaction is complete? Why is excess of nitrous acid undesirable?

39. Arrange the following amines in order of decreasing ease of their diazotization (under comparable conditions): *p*-toluidine, *p*-nitroaniline, 2,4-dinitroaniline, 2,4-dimethylaniline.

40. What factors affect the course of the diazotization of an aromatic amine? Explain your reasons.

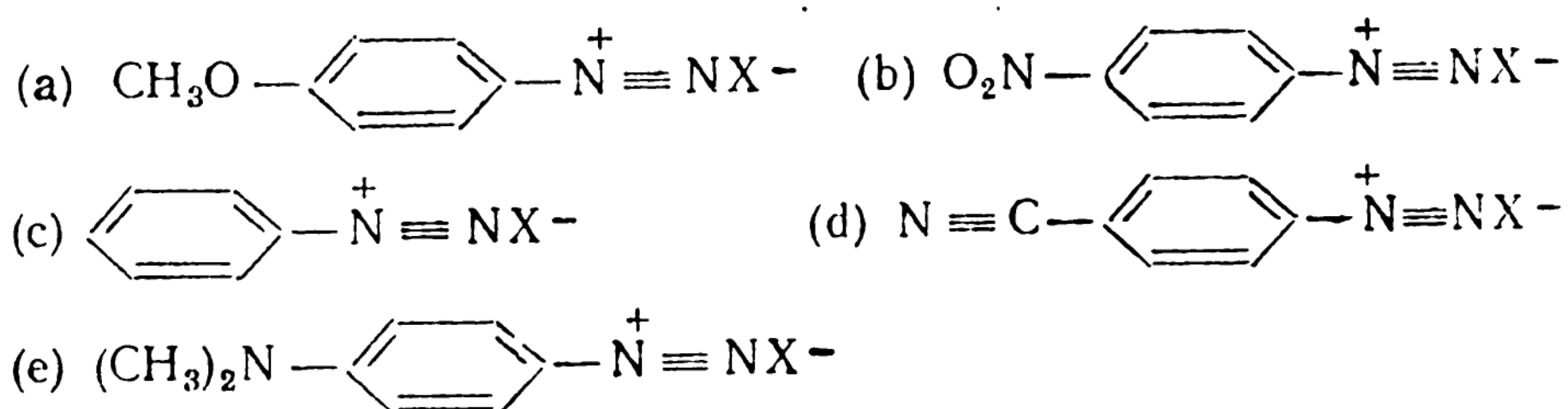
41. What methods can be used to prepare diazonium salts in the solid state?

42*. What conversions are brought about with diazonium chlorides by the successive action of moist silver oxide, alkali and then of acid? How could these conversions be accounted for?

43*. The diazotization of aniline gave a yellow precipitate instead of a transparent solution. What error was introduced in carrying out the reaction?

3. STABILITY AND STRUCTURE OF DIAZO COMPOUNDS

44. Arrange the following diazonium salts in order of increasing thermal stability:

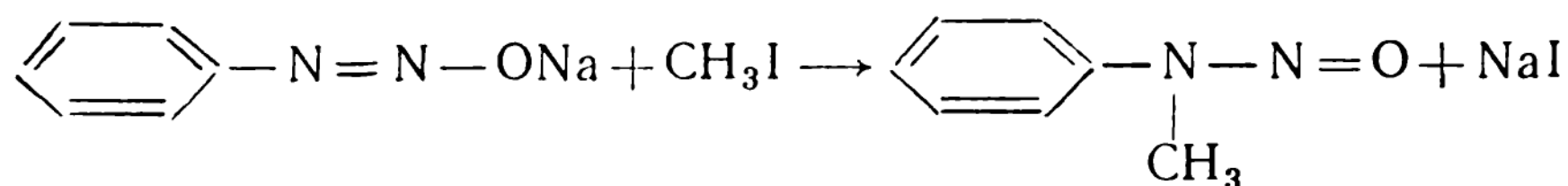
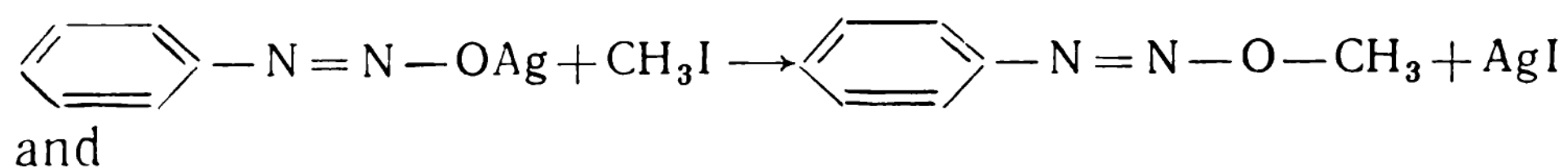


Explain your reasons.

45. How could you account for the difference in the stability of diazonium salts obtained from primary aromatic and aliphatic amines? Which of them and under what conditions can survive for some time?

46. Which of isomeric nitrophenyldiazo compounds (*o*-, *m*- or *p*-) decomposes most easily with the liberation of nitrogen?

47*. How could you account for the fact that the interaction of methyl iodide with silver and sodium diazotates leads to different products:



48. To what class of compounds does diazonium hydroxide resulting from the action of moist silver oxide on phenyldiazonium chloride belong? Explain what happens with it on standing.

49. What is the difference in the structure (and hence in the reactivity) of each of the following pairs of compounds: (a) phenyldiazonium diazohydrate and borofluoride; (b) *p*-tolyldiazonium cyanide and chloride?

50. Why are the hydrates of phenyldiazonium oxides called pseudo acids and diazohydrates (diazo acids), pseudo bases?

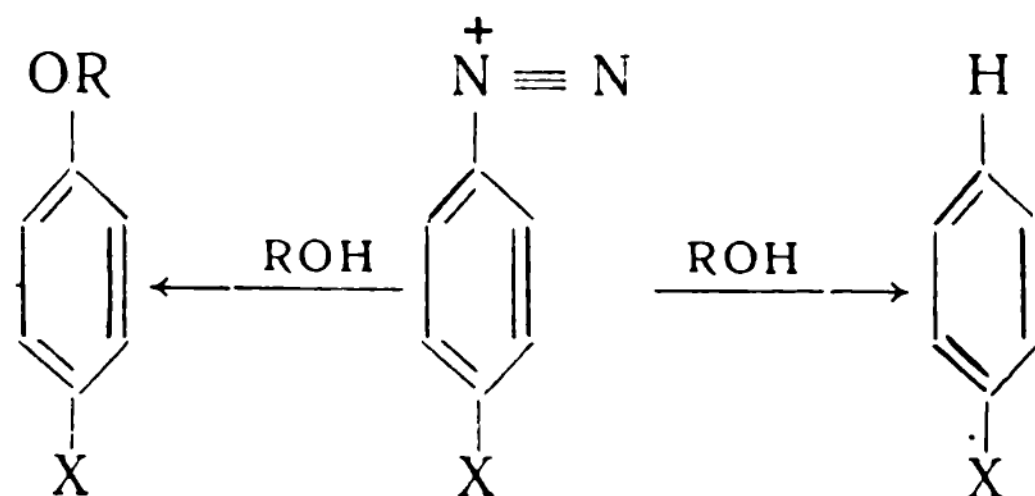
4. SUBSTITUTION REACTIONS OF THE DIAZO GROUP

51*. What side products can be formed in the reaction of displacement of the diazo group proceeding by the homolytic mechanism? Explain your reasons.

52. What is the role played by a cuprous salt in the reactions of exchange of the diazo group according to Sandmeyer?

53. Why does the displacement of the diazo group by chlorine or bromine proceed not so smoothly as by iodine?

54*. It is known that alcohols react with diazonium salts in a dual manner: with the formation of alkoxy derivatives (phenol esters) or with the displacement of the diazo group by hydrogen (the alcohol being oxidized to an aldehyde).

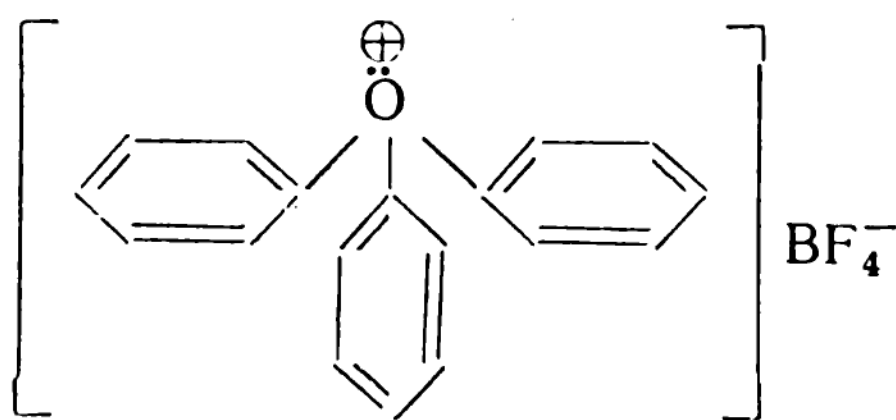


How will the ratio of the products of both reactions change if the following groups are in the *para*-position to the diazo group in the starting aryldiazonium salt: $-\text{NO}_2$, $-\text{OCH}_3$, $-\text{SO}_3\text{H}$, $-\text{N}(\text{CH}_3)_2$? Explain your reasons.

55*. How will the yield of an alkoxy derivative change in the interaction of phenyldiazonium chloride with ethyl, propyl, and amyl alcohols?

56. Why are the methods used for the displacement of the diazo group by iodine, bromine, and chlorine inapplicable for preparing aryl fluorides? What method of displacing the diazo group by fluorine do you know?

57. It is known that the decomposition of phenyldiazonium borofluoride in the presence of diphenyl ether results in the formation of triphenyloxonium borofluoride:



How could you account for its formation?

58*. Why is it necessary to use absolutely dry salts in the synthesis of fluoroderivatives by the Schiemann reaction (thermal decomposition of diazonium borofluorides)?

59. The displacement of the diazo group by hydrogen can be brought about by the action of alcohols and aqueous solutions of formaldehyde on aryldiazonium salts. Compare these methods and give your comments concerning the mechanism of the corresponding conversions.

60*. Why are phenyldiazonium sulphates rather than its bromides and chlorides used as the starting material in the displacement of the diazo group by the hydroxyl with the formation of phenols?

61. Enumerate the methods of displacement of diazo groups by the sulphohydryl group and by the sulpho group.

62*. How do diazonium halides react with alkenes and dienes in the presence of copper salts?

63. How is the synthesis of symmetric diaryls from aryl diazoniums brought about? Give examples. What other methods of preparing diaryls do you know?

64*. What methods of displacing the diazo group by aryl radicals do you know? Discuss their specific features.

65. How is the synthesis of asymmetric diaryls brought about with the aid of diazonium salts? Give concrete examples.

66*. Give examples of the arylation of metal salts with diazonium salts (the Nesmeyanov reaction).

5. AZO COUPLING REACTIONS

67*. What experimental facts indicate that azo coupling is a reaction of electrophilic substitution in the aromatic ring?

68. What is the essence of present-day conceptions of the mechanism of the azo coupling reaction? Give experimental data supporting this mechanism.

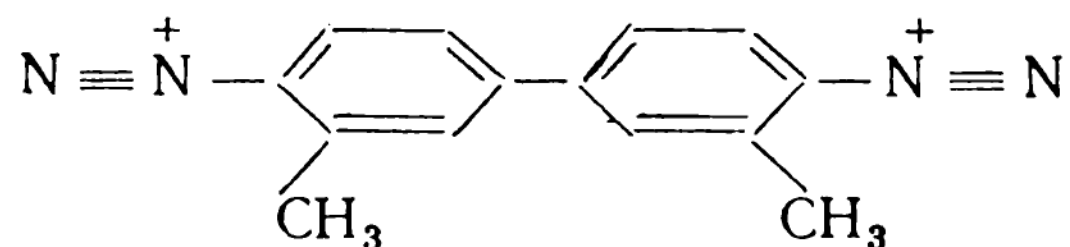
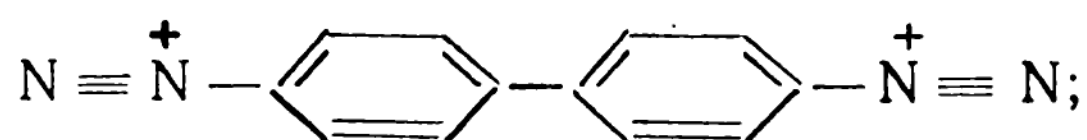
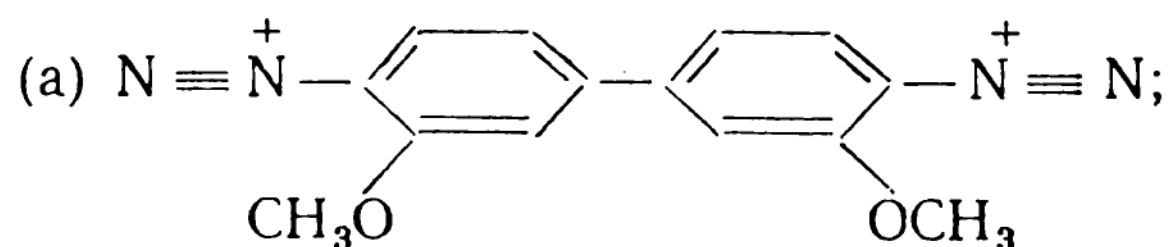
69*. Why is the azo coupling reaction usually brought about at pH = 5-9? What complications may arise if the value of pH is not maintained within the indicated limits?

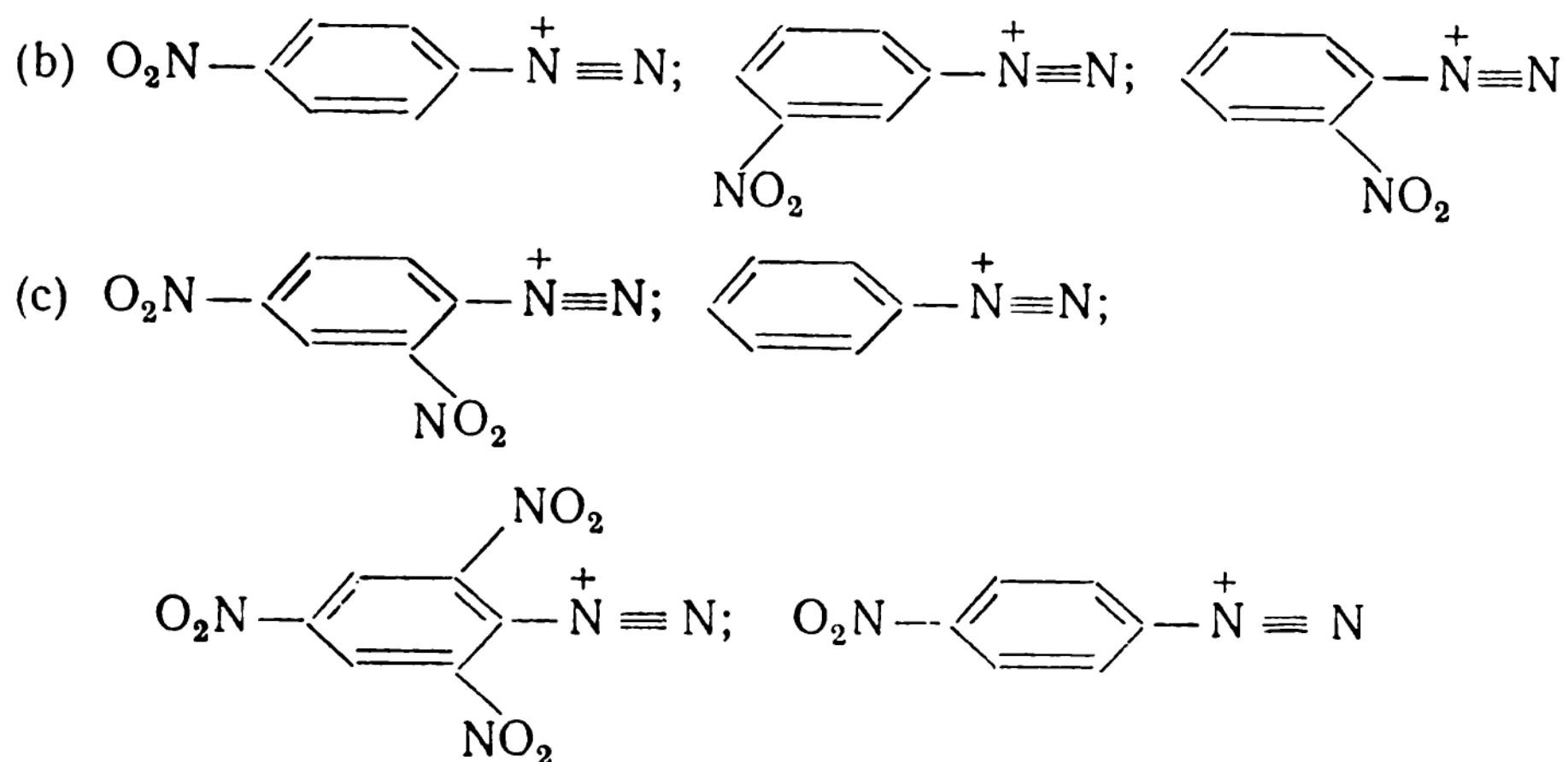
70. In the azo coupling reaction, just as during the sulphonation reaction, there is observed an isotopic effect. What inferences could be made on this basis?

71. Why should the reaction of azo coupling with phenols be carried out in a weakly alkaline medium (pH = 9) and with amines, in a weakly acidic medium (pH = 5-6)?

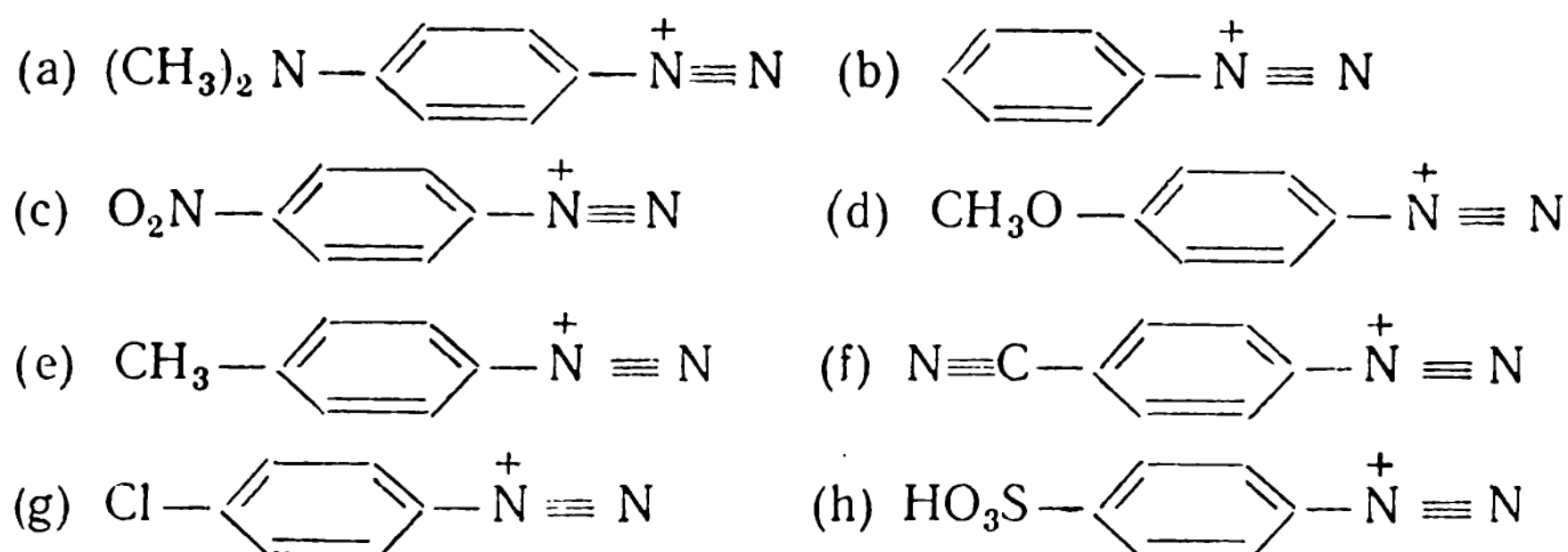
72. Explain why the diazonium salt obtained from picramide couples with a larger number of azo components than the phenyldiazonium salt.

73. Arrange the following diazo compounds in order of increasing activity in azo coupling reactions (under identical conditions):





74. Arrange the following diazo compounds in order of decreasing activity in azo coupling reactions (under identical conditions):



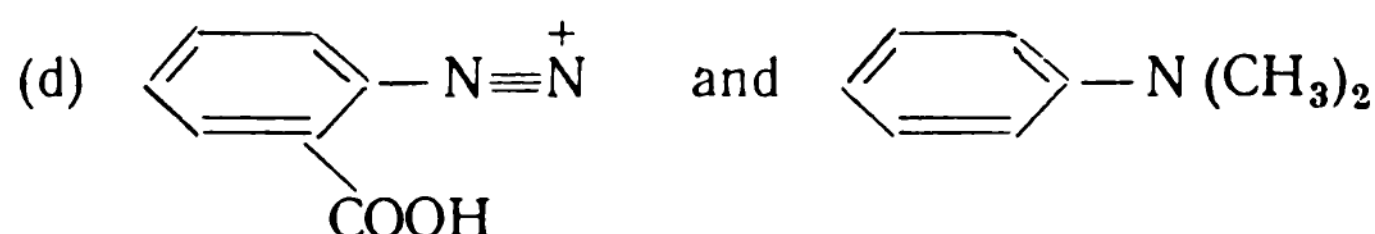
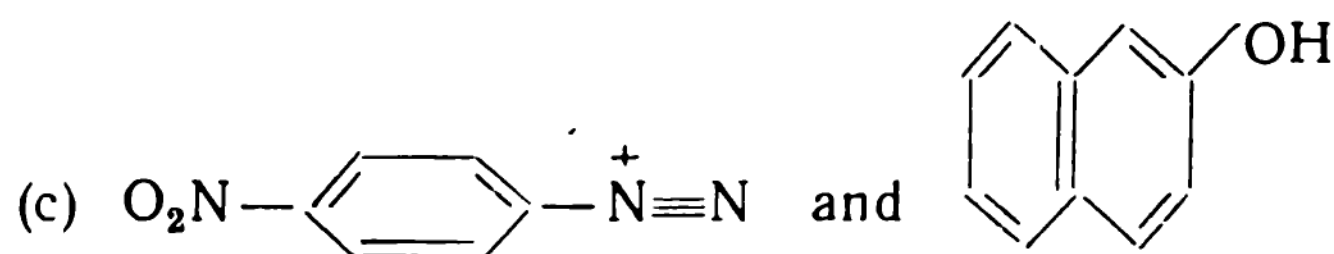
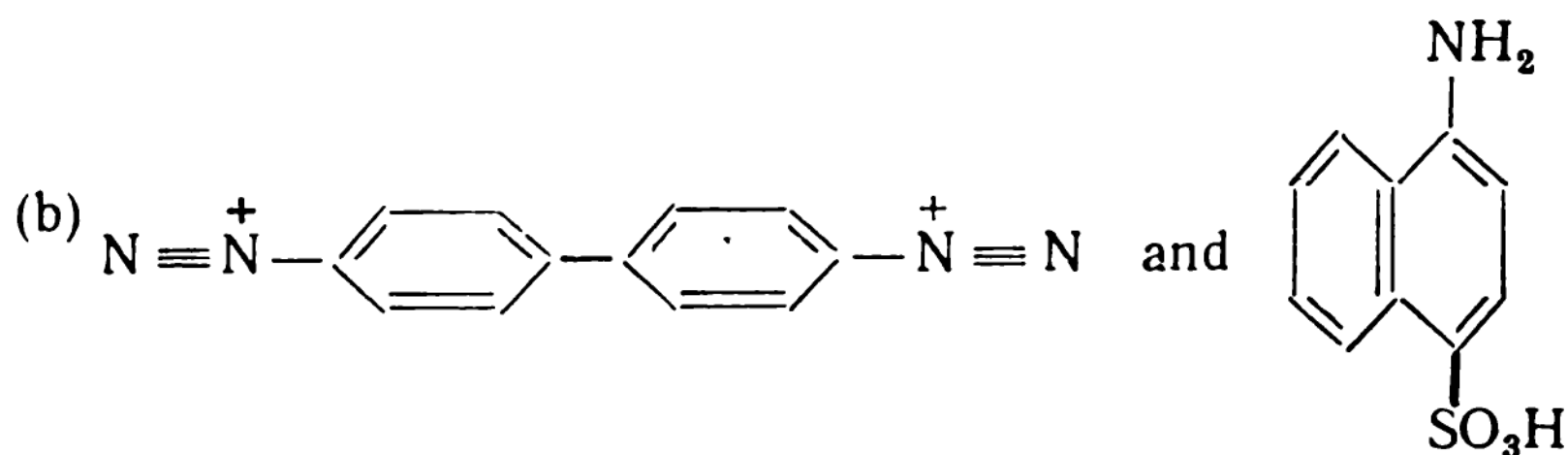
75*. Which of the three isomeric phenylenediamines enters most readily into the azo coupling reaction?

76. Which of the compounds indicated below will enter into the azo coupling reaction at pH = 5 with the salts of: (a) phenyldiazonium; (b) anisyldiazonium; (c) 2,4,6-trinitrophenyldiazonium? The compounds are as follows: *m*-phenylenediamine, anisole, aniline, mesitylene, dimethylaniline, phenol, *p*-aminophenol, *p*-cresol.

77*. Which of the following amines enters more readily into the azo coupling reaction: N,N-dimethylaniline; N,N,2,6-tetramethylaniline? Explain the cause.

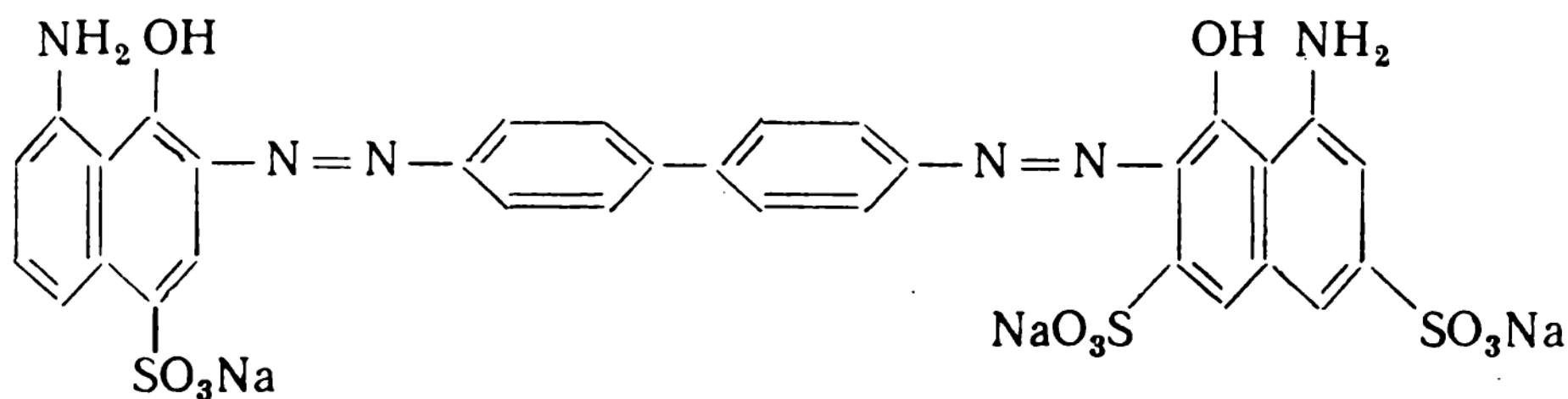
78. Write the formulas of the azo dyes resulting from the coupling of:



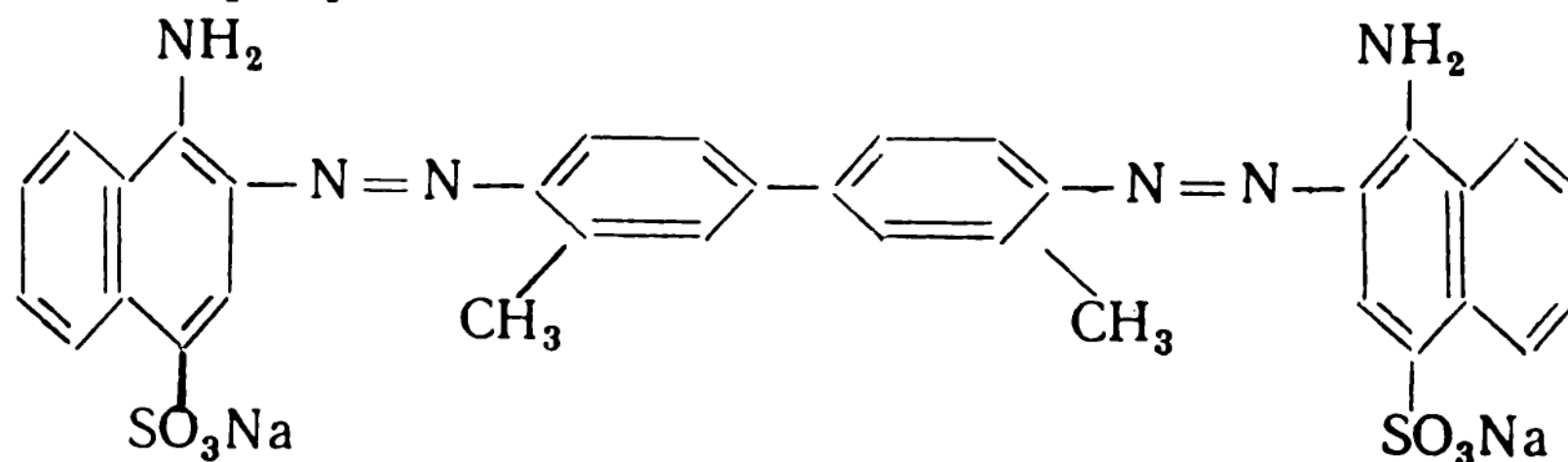


79. What compounds were used to prepare the following in the azo coupling reaction:

(a) direct diazo black

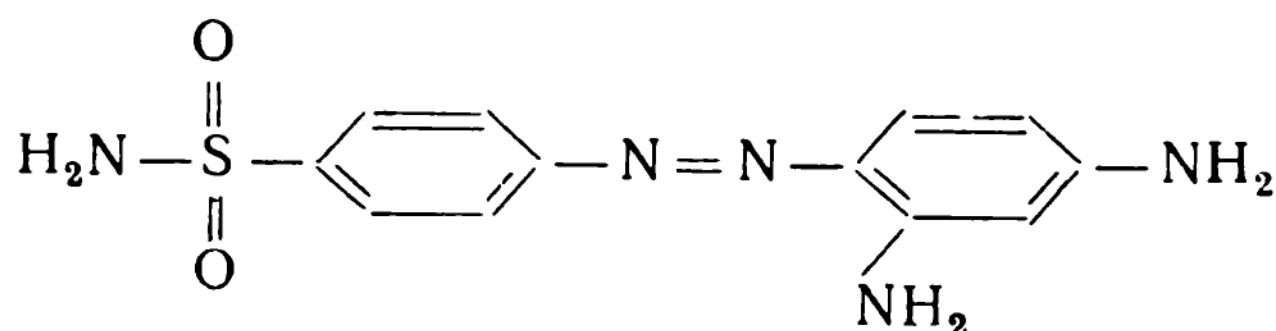


(b) benzopurpurin

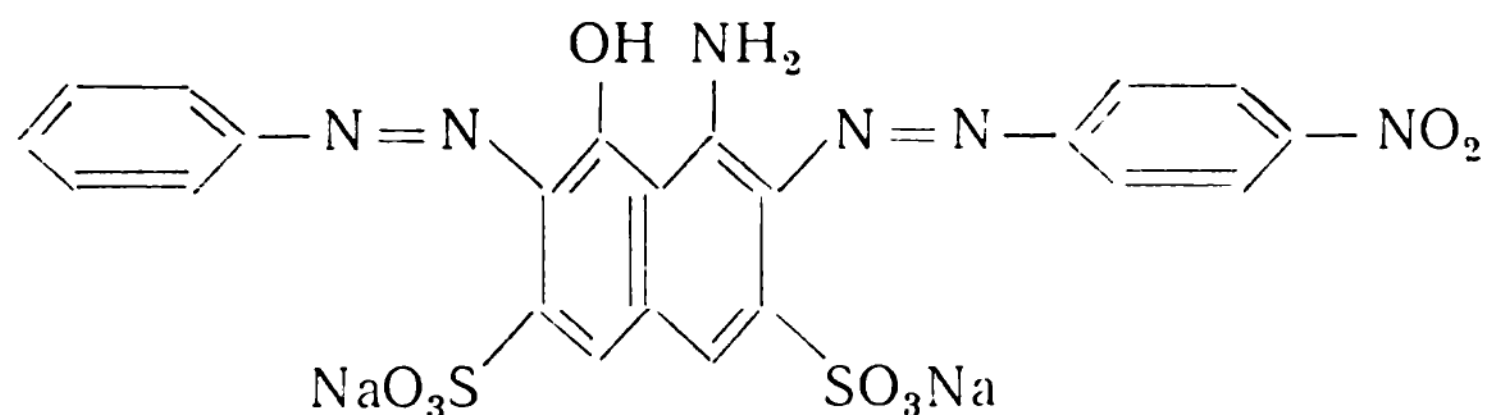


In what medium was the coupling reaction conducted in the first and in the second case?

80*. Suggest a method of preparing red streptocide from benzene:

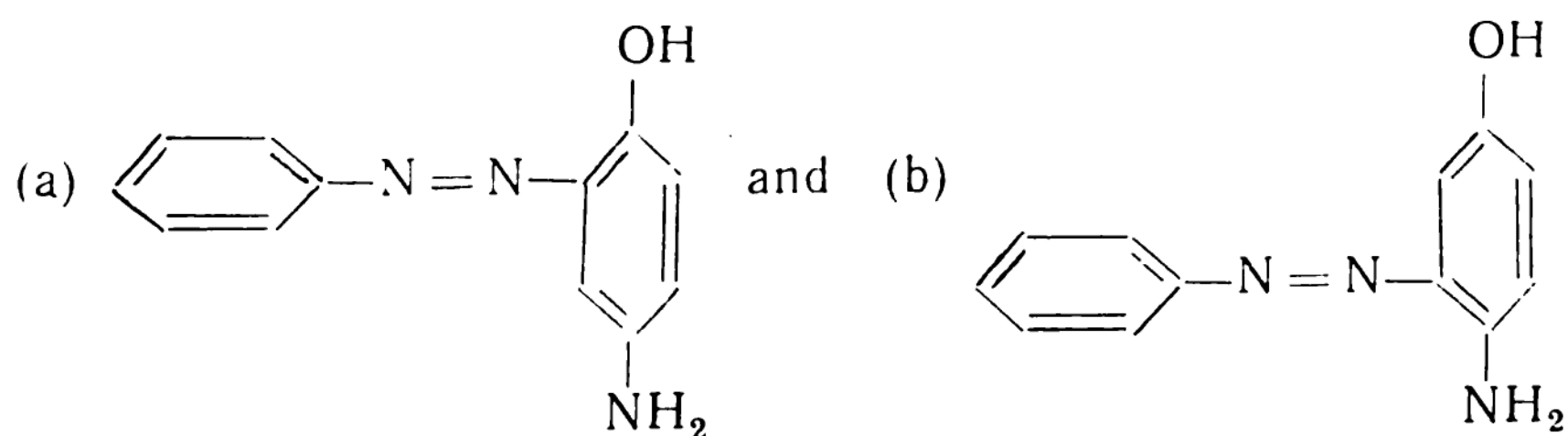


81. What method can be used to prepare from H-acid (1-amino-8-hydroxynaphthalene-3,6-disulphoacid), aniline and *p*-nitroaniline the following azo dye:



Indicate the approximate value of pH of the reaction mixture at each step of the reaction.

82. Under what conditions must the azo coupling reaction of phenyldiazonium with *p*-aminophenol be carried out in order to prepare the following compounds:



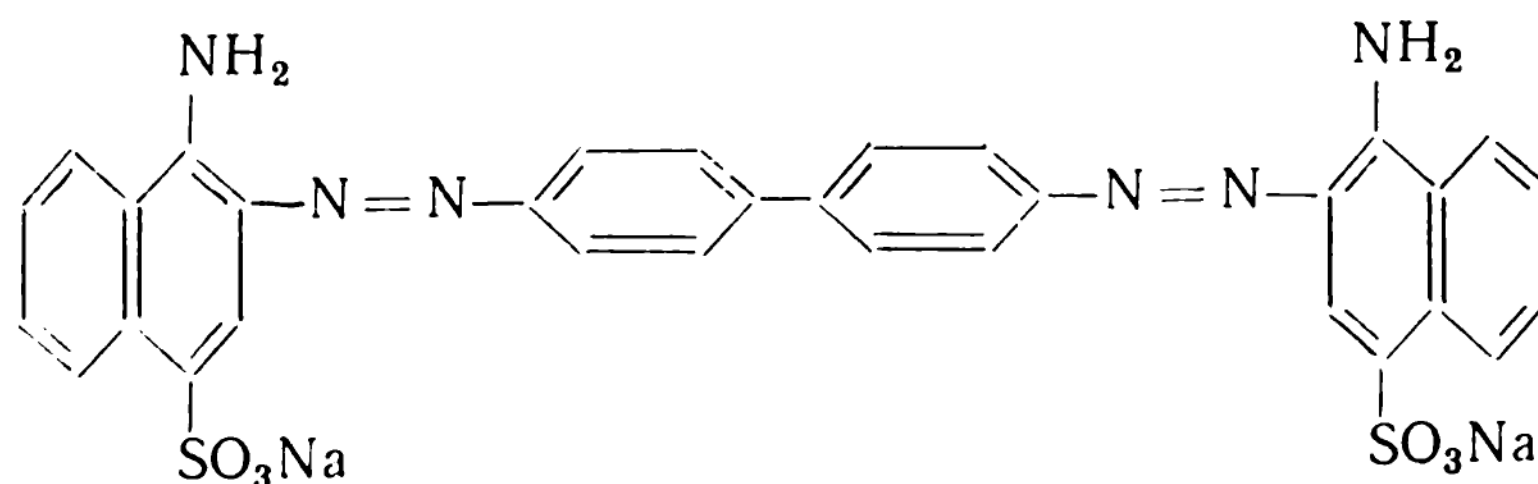
83*. Write the formulas of helianthin (in acidic and alkaline solutions). What is the cause of the change of its colour with changing pH?

84. Write the structural formulas of the dye congo in alkaline and mineral-acid media.

85*. Why are *o*-hydroxy azo compounds insoluble in alkalis and distilled with the vapour?

86*. Enumerate and describe methods of applying an azo dye onto the fabric. Name the dyes that are applied on the fabric by each of the methods indicated.

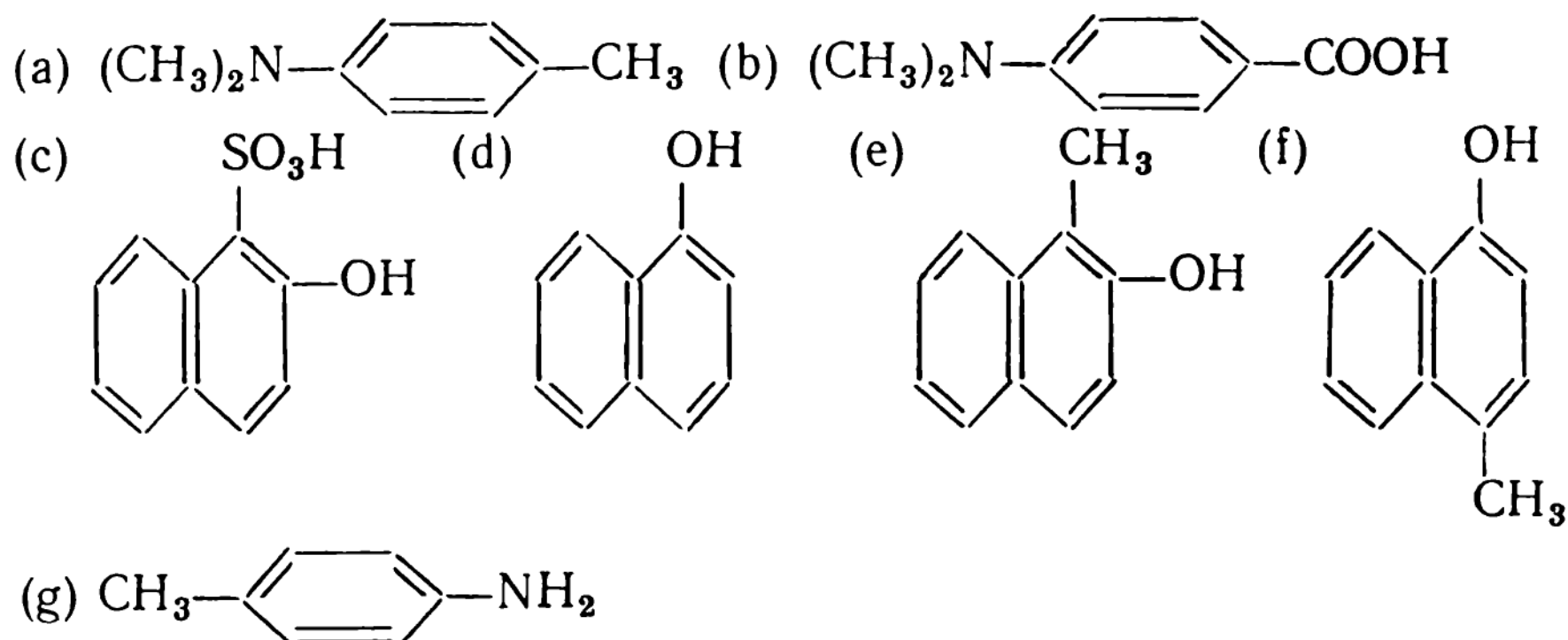
87. Prepare benzopurpurin from benzene and naphthalene:



88. How can *p*-nitroaniline red be prepared from benzene and naphthalene?

89. How can methyl orange be made from benzene and methanol?

90*. Write what azo compounds result from the coupling of phenyldiazonium chloride with the following azo components:



In what medium should the reaction be carried out in each case?

91. How will H-acid (1-amino-8-hydroxynaphthalene-3,6-disulphoacid) react with *p*-nitrophenyldiazonium chloride at pH = 9 and pH = 5?

92. The reaction mixture obtained after azo coupling must not contain an excess of one component with respect to the other. How can this be checked experimentally?

93*. What is the diazotype?

6. USE OF DIAZO COMPOUNDS FOR PREPARATIVE PURPOSES

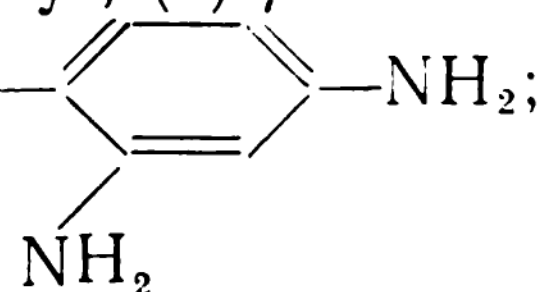
In solving the synthetic problems given below it is necessary to make a skilful use of certain reactions characteristic of nitro compounds, diazo compounds and also of the intermediate products of reduction of the nitro group. The most important of these reactions are as follows: (a) the partial reduction of a dinitro compound; (b) the elimination of the diazo group on interaction with alcohols; (c) the heterolytic decomposition of diazonium borofluorides in the presence of other aromatic compounds; (d) the displacement of the diazo group by the nitro group; (e) the hydrogenolysis

of the $\text{N}=\text{N}$ bond of the azo group with the formation of amino groups; (f) the displacement of the diazo group by the $-\text{C}\equiv\text{N}$ group and its subsequent hydrolysis; (g) the preparation of symmetrical derivatives of diphenyl according to the scheme: benzene $\rightarrow$ nitrobenzene $\rightarrow$ hydrazobenzene $\rightarrow$ benzidine.

94. Prepare the following compounds from benzene and inorganic reagents: (a) 4,4'-diiododiphenyl*; (b) 1,2,3-tribromobenzene*; (c) *m*-fluorochlorobenzene; (d) *m*-nitrophenylhydrazine; (e) 1,3,5-tribromobenzene; (f) 3-nitrodiphenyl*.

95*. Using benzene, acetic acid and inorganic reagents, prepare the following: (a) *p*-nitrophenylhydrazine; (b) *p*-dinitrobenzene; (c) magneson-1 (*p*-nitrobenzeneazoresorcinol); (d) cadion (*p*-nitrophenylazoaminobenzene); (e) 3,4,5-triiodonitrobenzene; (f) terephthalic acid; (g) *p*-nitrobenzoic acid.

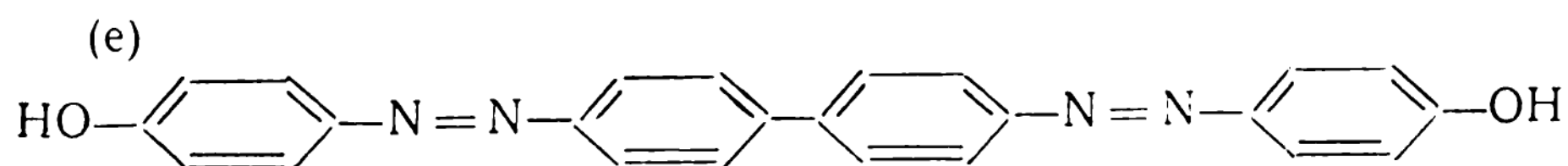
96. Prepare the following compounds from benzene and inorganic reagents: (a) 4,4'-dihydroxydiphenyl; (b) *p*-benzoic acid; (c) chrysoidine, $\text{C}_6\text{H}_5-\text{N}=\text{N}-$



and (d) pentabromobenzene*.

97. By using benzene and inorganic reagents prepare the following compounds: (a) *o*-bromofluorobenzene; (b) *p*-hydroxyazobenzene; (c) 3,4-diiodobenzoic acid; (d) atoxyl (4-aminobenzenearsonic acid); and (e) *m*-aminophenol.

98. Prepare the following compounds from benzene and inorganic reagents: (a) *m*-hydroxybenzonitrile; (b) 2,6-dinitrophenol; (c) 2,4,6-tribromofluorobenzene*; (d) *m*-dichlorobenzene;



99. Prepare the following compounds from benzene and inorganic reagents: (a) 2,4-dinitrofluorobenzene; (b) *m*-nitroiodobenzene; (c) *p*-carboxyphenylhydrazine; and (d) 2,4,6-tribromothiophenol.

100. Using benzene and inorganic reagents, prepare the following compounds: (a) *m*-aminobenzoic acid; (b) *m*-bromoaniline; (c) 4-hydroxyazobenzene; (d) 4-bromodiphenyl.

101. Using benzene, methanol and inorganic reagents, prepare the following compounds: (a) 3-nitro-4-dimethylaminoazobenzene; (b) *m*-chloroanisole; (c) 2,2'-dimethoxydiphenyl*; (d) *m*-hydroxydimethylaniline.

102. Prepare the following compounds from benzene and inorganic reagents: (a) *m*-anisic (*m*-methoxybenzoic) acid*; (b) 4-dimethylaminoazobenzene; (c) guaiacol (*o*-methoxyphenol); (d) *N,N*-dimethyl-*p*-phenylenediamine; (e) methyl *p*-thiosalicylate.

103. Using toluene and inorganic reagents, prepare the following compounds: (a) *p*-tolylhydrazine; (b) 3-bromo-4-iodobenzoic acid*; (c) *p*-fluorotoluene*; (d) 3,5-diiodo-*p*-cresol*; (e) 3,5-dibromotoluene*.

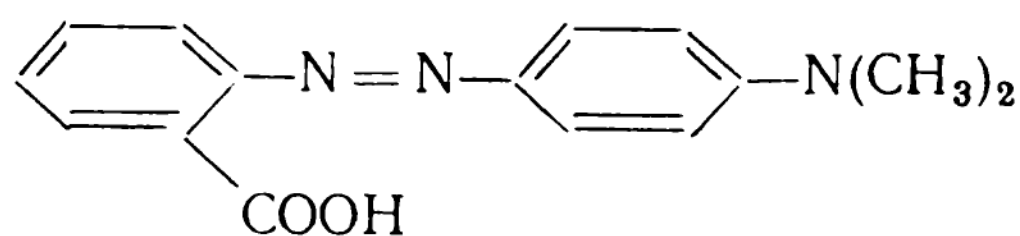
104*. Using toluene, acetic acid and inorganic reagents, prepare the following compounds: (a) *m*-toluidine; (b) 3,3'-ditolyl; (c) *m*-iodobenzoic acid; (d) *m*-toluic acid.

105. Prepare the following compounds from nitrobenzene and inorganic reagents: (a) 4,4'-difluorodiphenyl; (b) 1,3,5-tribromobenzene; (c) 1-fluoro-2,4,6-tribromobenzene*; (d) *m*-bromophenol*.

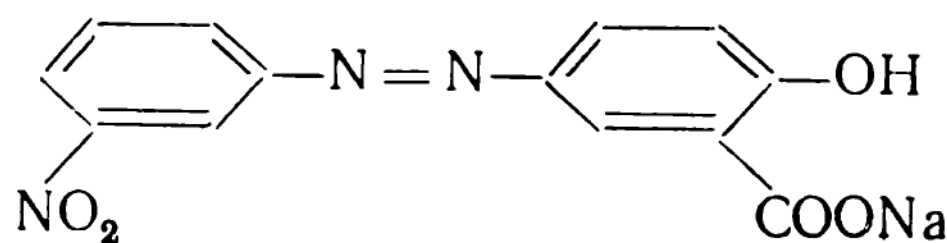
106. Using aniline, acetic acid and inorganic reagents, prepare the following compounds: (a) 3,4,5-triiodonitrobenzene; (b) *p*-dinitrobenzene; (c) terephthalic acid; (d) *p*-nitrobenzoic acid.

107. Prepare the following compounds from *p*-nitroaniline and inorganic reagents: (a) *m*-bromoaniline; (b) 1-fluoro-3,5-dibromobenzene; (c) 1-fluoro-4-iodobenzene; (d) *p*-fluorophenol.

108*. Using phthalic anhydride, benzene, methyl iodide and inorganic reagents, prepare methyl red:



109*. Using benzene, toluene, and inorganic reagents, prepare alizarin yellow:



110*. Prepare 2,4- and 3,4-diaminophenols from *p*-nitrophenol, aniline and inorganic reagents.

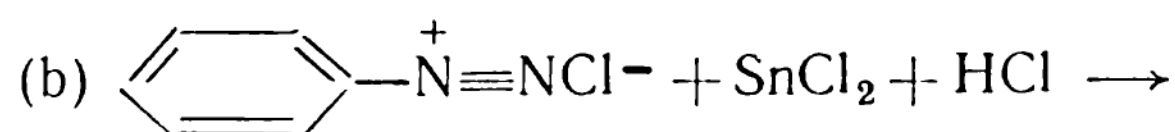
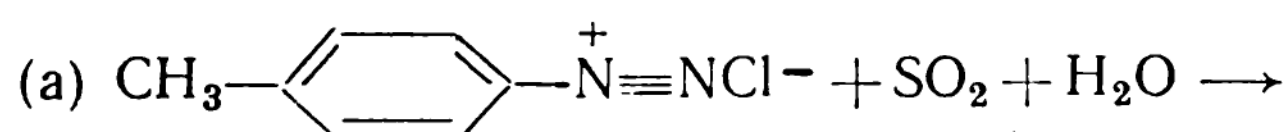
111*. Prepare 1-(*p*-nitrophenyl)-buta-1,3-diene from ethyl alcohol, *p*-nitroaniline and inorganic reagents.

112*. Prepare 2',4',6'-trinitro-2,4,6-trimethylazobenzene from benzene, acetone and inorganic reagents.

113*. Prepare symmetrical and unsymmetrical diphenylhydrazines from nitrobenzene.

114. Suggest the most expedient route of synthesis of all the isomeric nitrobromobenzenes, bromoanilines, toluidines, and benzenedisulphoacids.

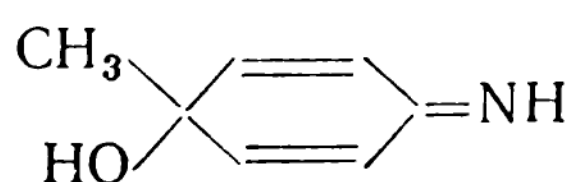
115*. Complete and balance the following equations:



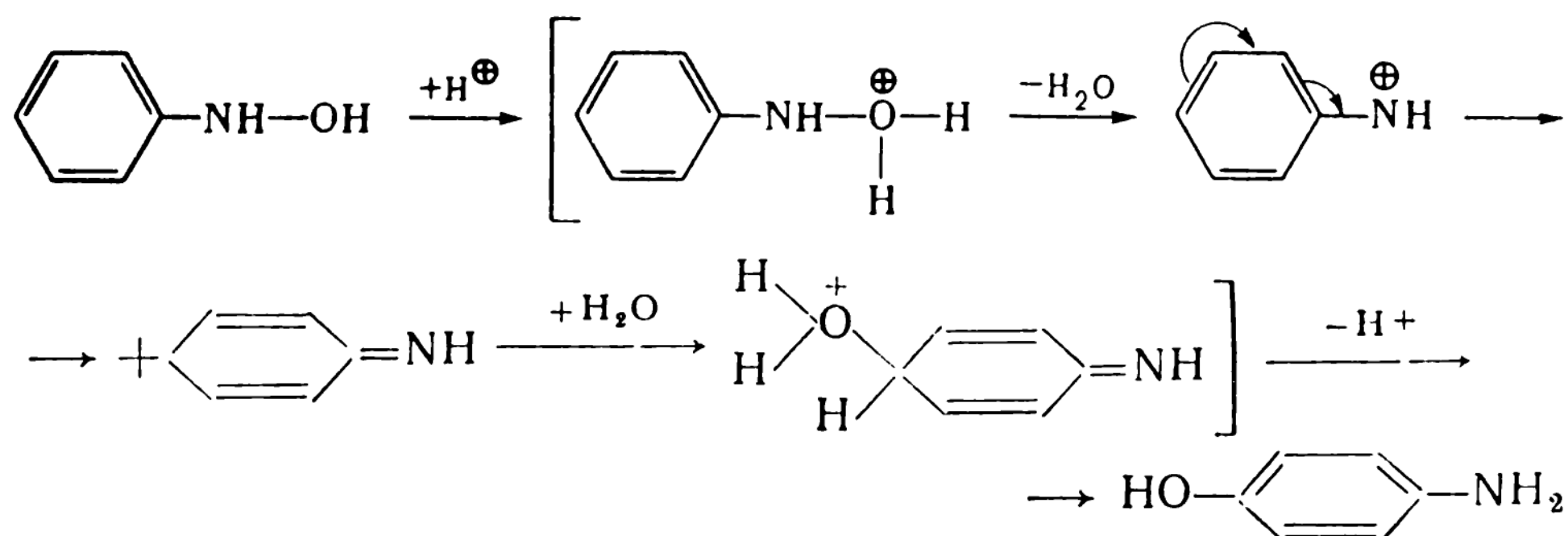
Answers

6. If phenylhydroxylamine is acted on by sulphuric acid, *p*-aminophenol is exclusively formed, while the action of concentrated hydrochloric acid results in the formation of a mixture of aminophenol and *p*-chloroaniline.

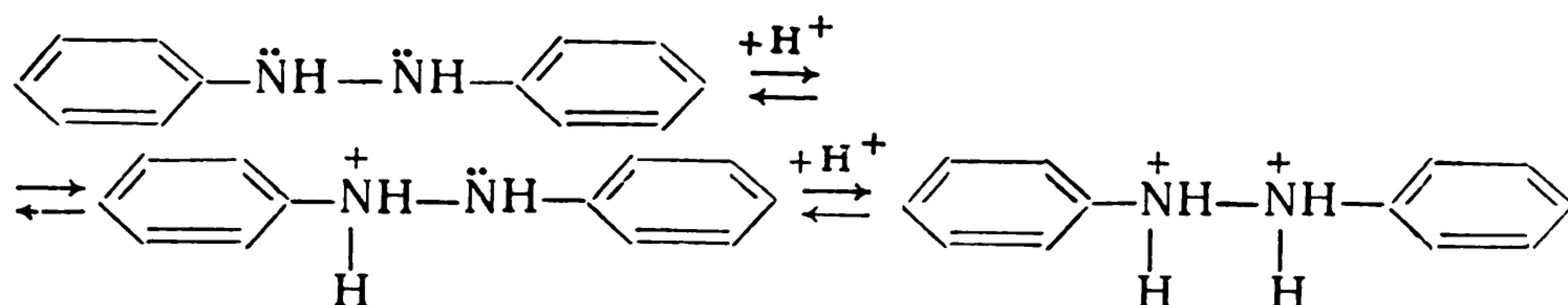
Under analogous conditions *p*-tolylhydroxylamine leads to quinolimine:



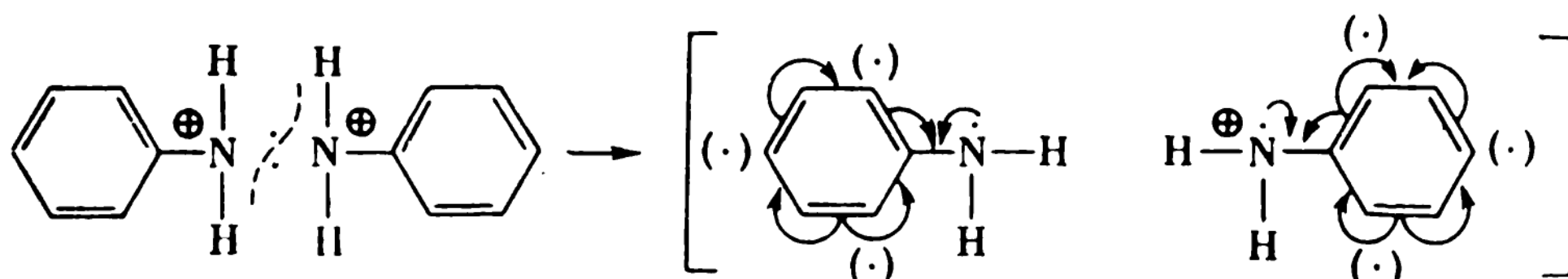
The supposed mechanism of conversions may be illustrated by taking as an example the preparation of *p*-aminophenol:



It is supposed that the rearrangement is preceded by the protonation of both nitrogen atoms:



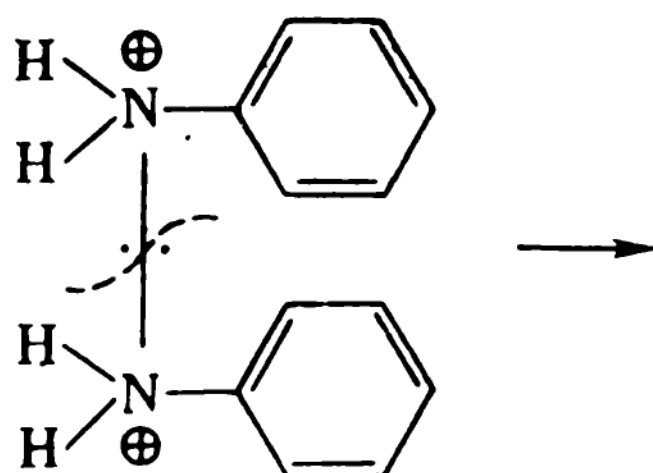
and also that the addition of the second proton determines the rate of the overall process and the rearrangement proceeds intramolecularly. As regards the subsequent steps there exist two opinions. According to the more probable one there takes place the homolytic cleavage of the —N—N bond leading to the formation of two radical-cations:

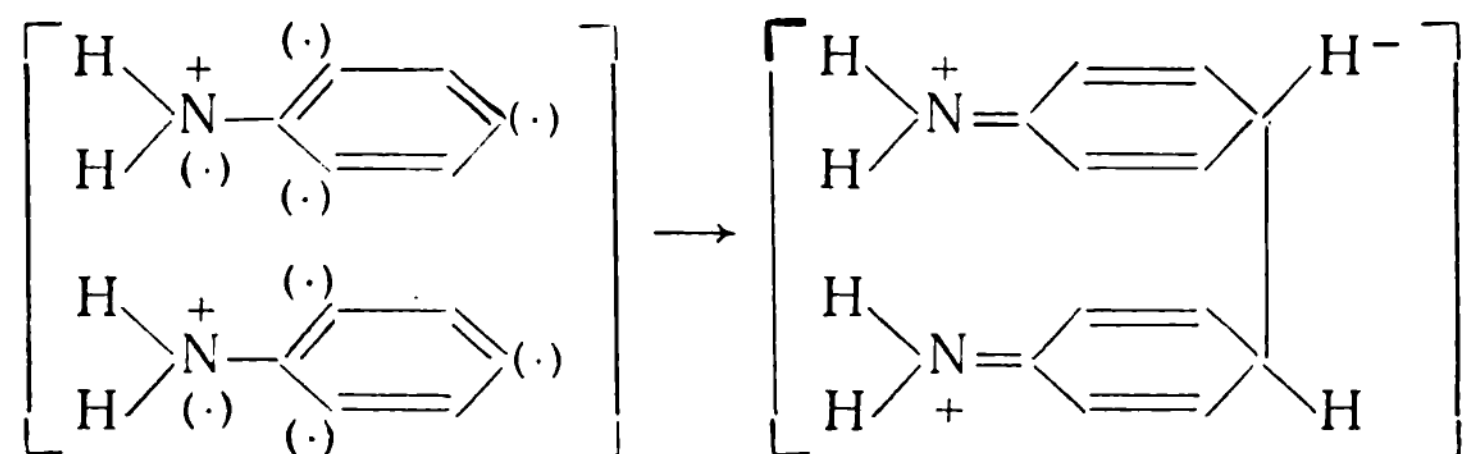


Since compounds containing an ammonium nitrogen have a tetrahedral structure, the benzene rings in the protonated benzidine are at a distance apart from each other that does not exclude the possibility of the overlap and interaction of their π -electrons.

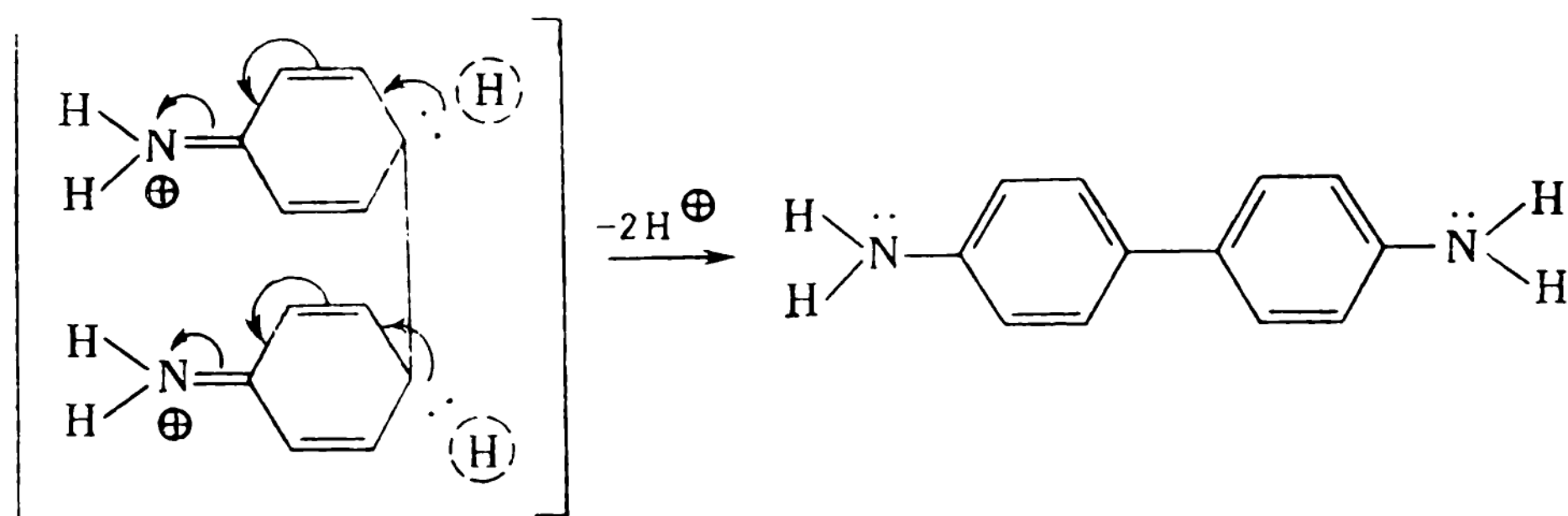
But unpaired electrons in both halves may, with approximately the same degree of probability, be on nitrogen atoms as well as in the *ortho*- and *para*-positions of both benzene rings.

The recombination of the two free-radical particles leads to the formation of a new carbon-carbon bond:

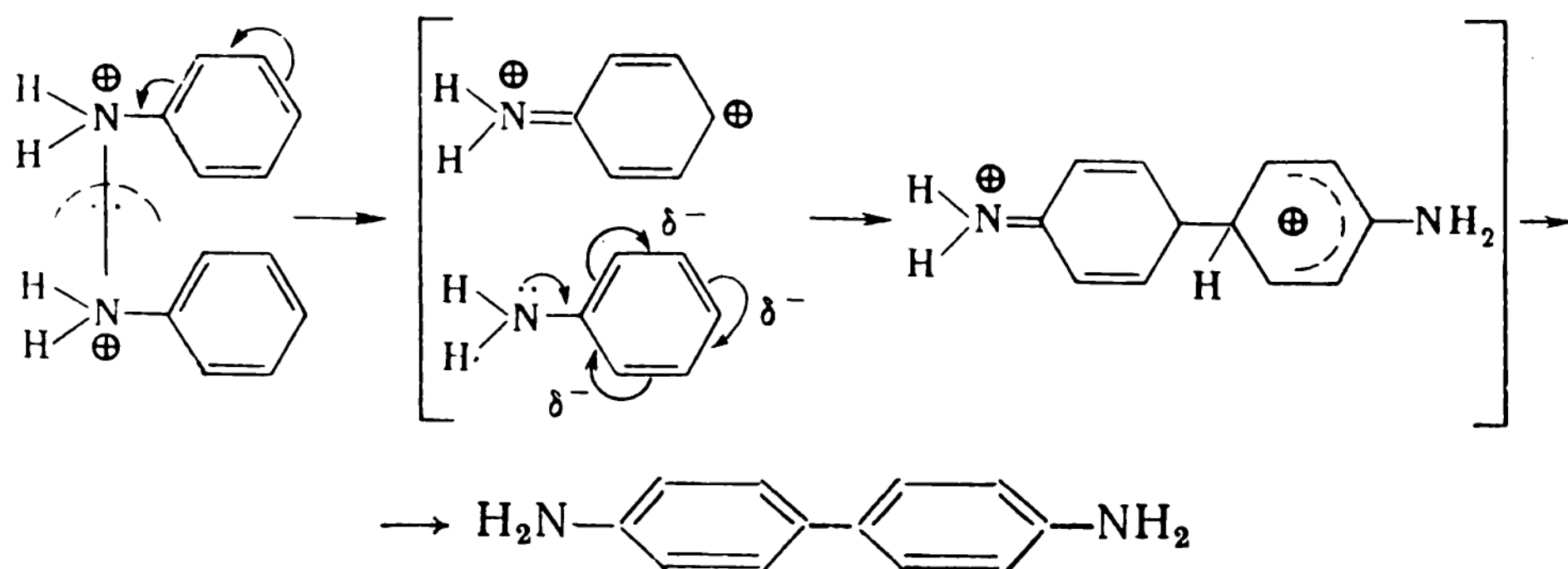




The rearrangement ends with the splitting off of protons and formation of benzidine:



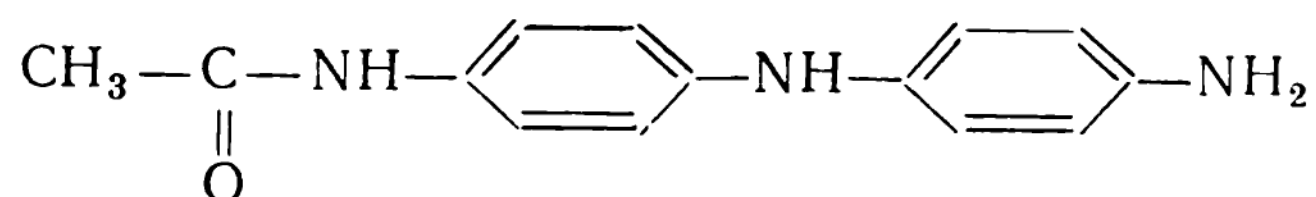
There exists another opinion, according to which the —N—N bond in the protonated benzidine is ruptured heterolytically:



Then there must be formed, as intermediates, a dication and an aniline molecule, in which the excess electron density is concentrated in *o*- and *p*-sites of the benzene ring. A new carbon-carbon bond is formed due to electrophilic attack by the dication across the *para*-position of aniline. A shortcoming of the second approach is lack of strict arguments in favour of the heterolytic cleavage of the N—N bond, i.e., the formation of a dication.

16. (a) There is predominantly formed the corresponding diphenylene (2,4'-diamino-5-chlorodiphenyl) containing as an impurity the product of *o*-semidine rearrangement (5-chloro-2-aminodiphenylamine) and benzidine, which results from the elimination of chlorine;

(b) there is exclusively formed *para*-semidine



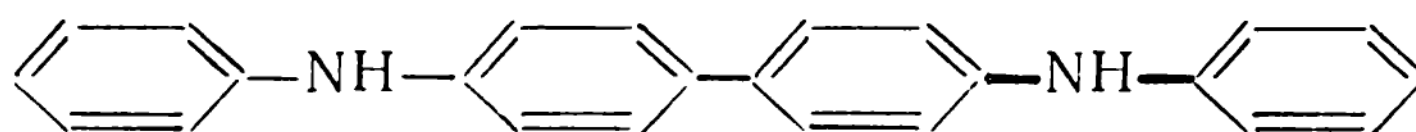
(c) only benzidine is formed; the carboxylic group is eliminated;

(d) only the product of *o*-semidine rearrangement is formed (2-amino-5-methyldiphenylamine);

(e) only the product of benzidine rearrangement—4,4'-diamino-3,3-dimethoxydiphenyl—is formed.

For more detail see C.K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., 1953.

18. There is formed *p',p'*-bis(diphenylamino)diphenyl



19. Azoxybenzene can be obtained by reducing nitrobenzene with sodium methoxide through the action of phenylhydroxylamine on nitrobenzene and by oxidation of azobenzene with hydrogen peroxide.

21. The molecule of the *trans*-isomer has a planar structure, as a result of which there appears the possibility of an interaction between the π -electrons of the N=N bond with the π -electrons of the benzene ring. The C—N bond becomes shorter (like the central double bond of butadiene).

In the *cis*-isomer molecule there arise steric hindrances, as a result of which the benzene rings are found to be turned 50° relative to the plane in which the azo group lies. This excludes the possibility of conjugation of the azo group with the π -electrons of the benzene rings and lowers the stability of the molecule. The C—N bond in the *cis*-isomer is no longer part of the conjugated system and therefore has a normal length.

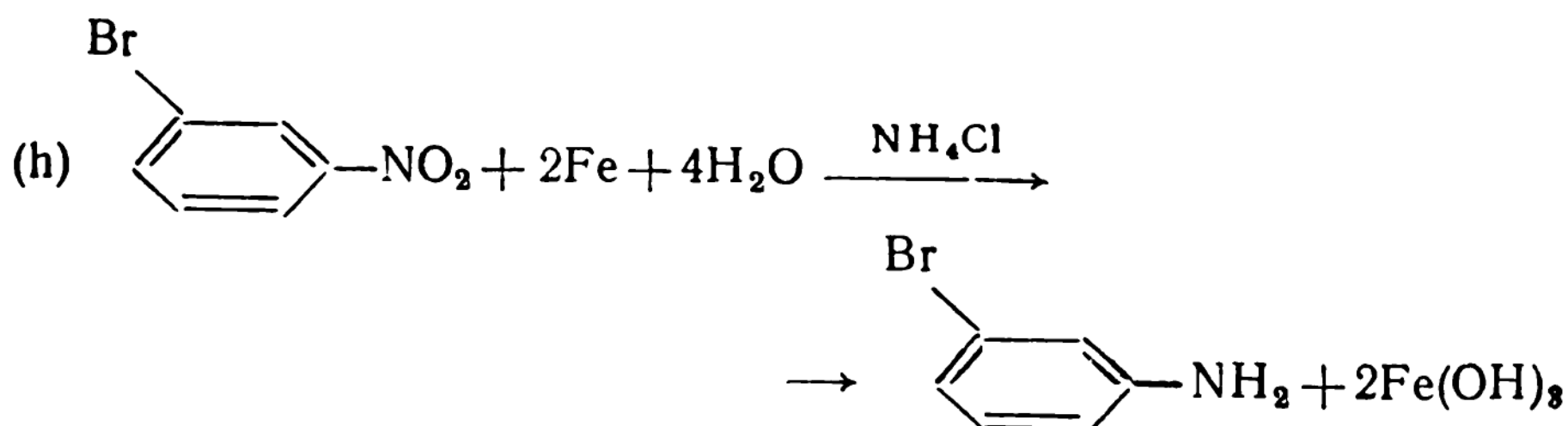
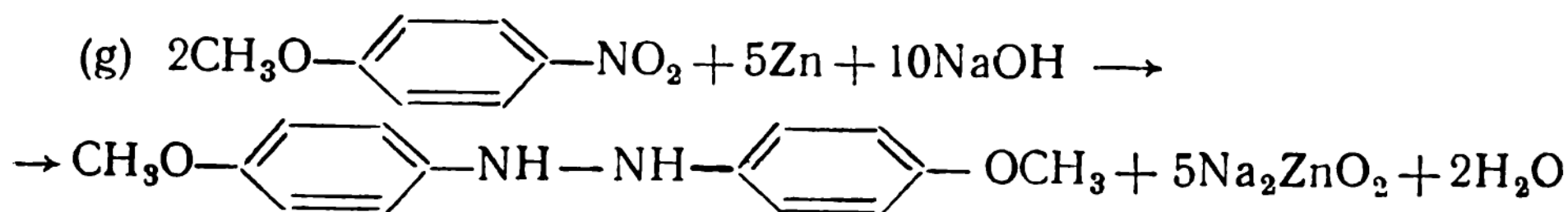
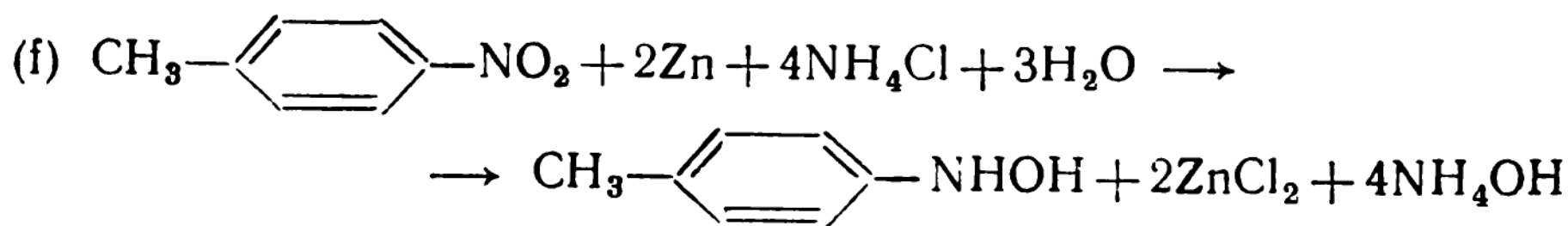
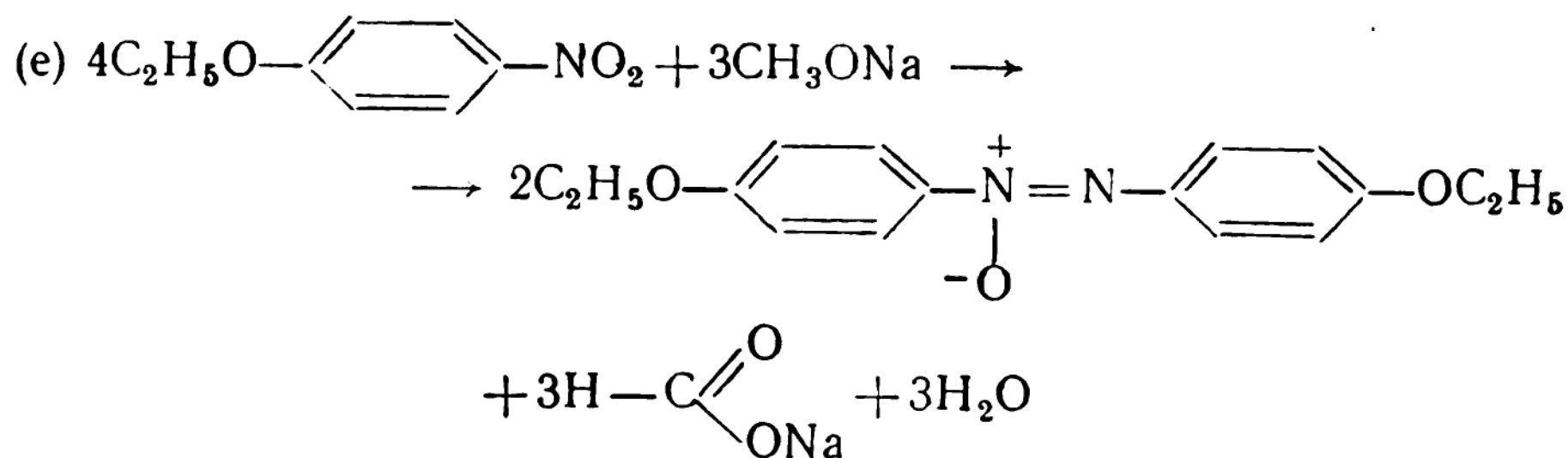
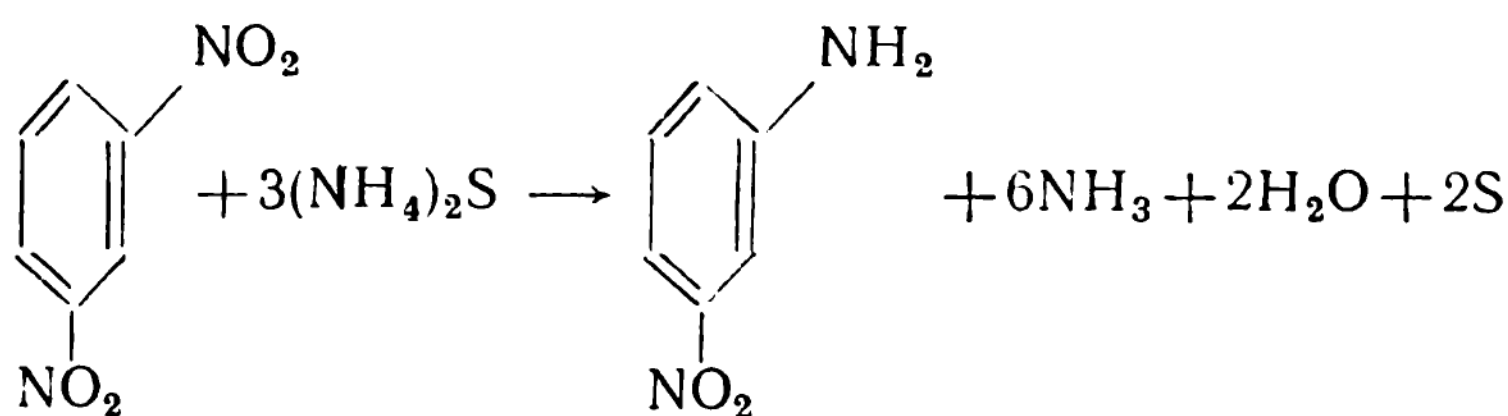
23. The reduction by hydrazine hydrate and skeleton nickel proceeds under mild conditions. The side products of the reac-

tion (gaseous nitrogen, water) do not interfere with the isolation of the resulting amines by simple distillation. The yields of the amines are as a rule high.

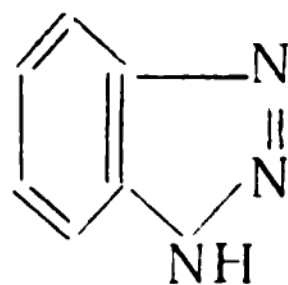
24. By the nitration of phenol there is obtained picric acid, which is reduced to picramic acid by the action of sodium sulphide.

26. Nitrobenzene is reduced to phenylhydroxylamine through the action of zinc dust in the presence of ammonium chloride. When acted on by sulphuric acid, phenylhydroxylamine rearranges into *p*-aminophenol.

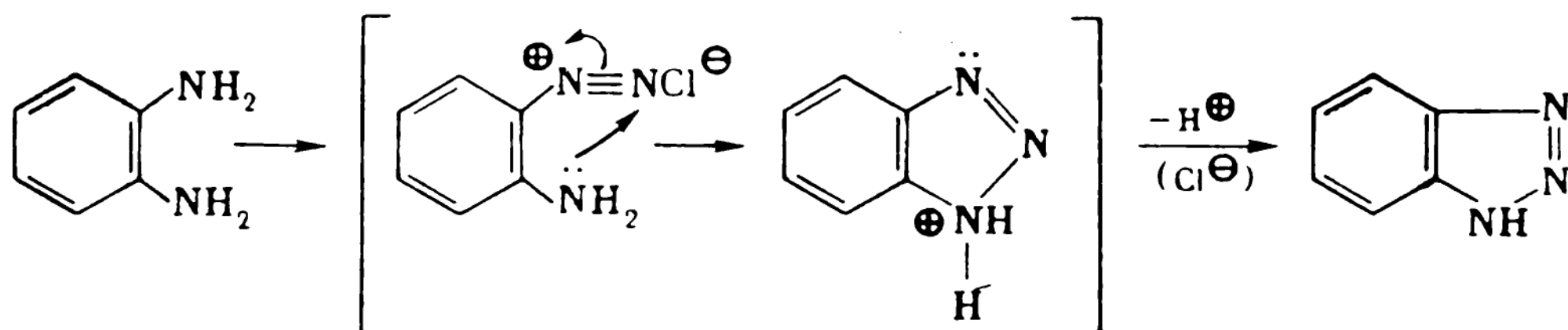
29. (a)



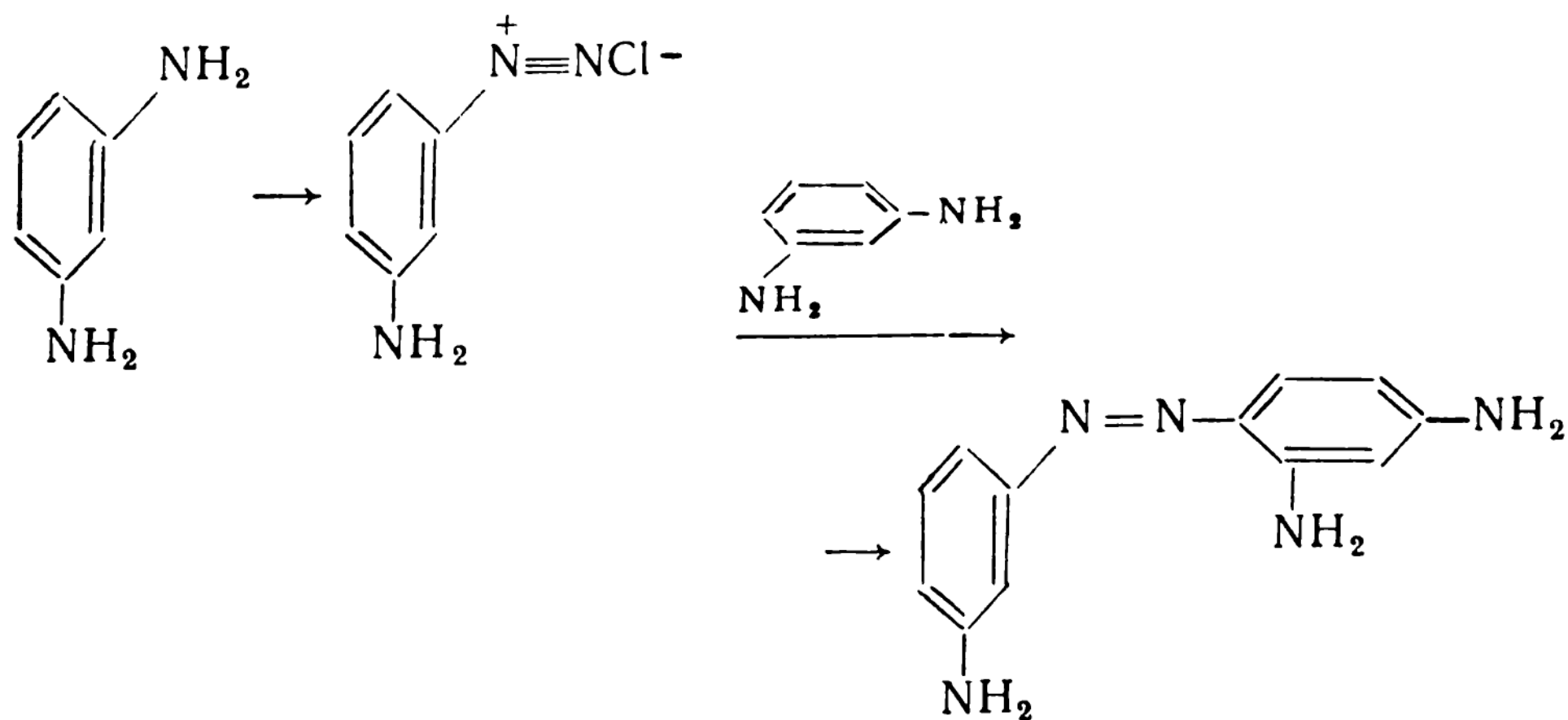
33. The diazotization of *ortho*-phenylenediamine usually leads to the formation of benzotriazole



This is accounted for by the fact that both amino groups cannot simultaneously react with the nitrosating agent—a monodiazonium salt is first formed, in which there takes place an intramolecular interaction between the diazo and amino groups:

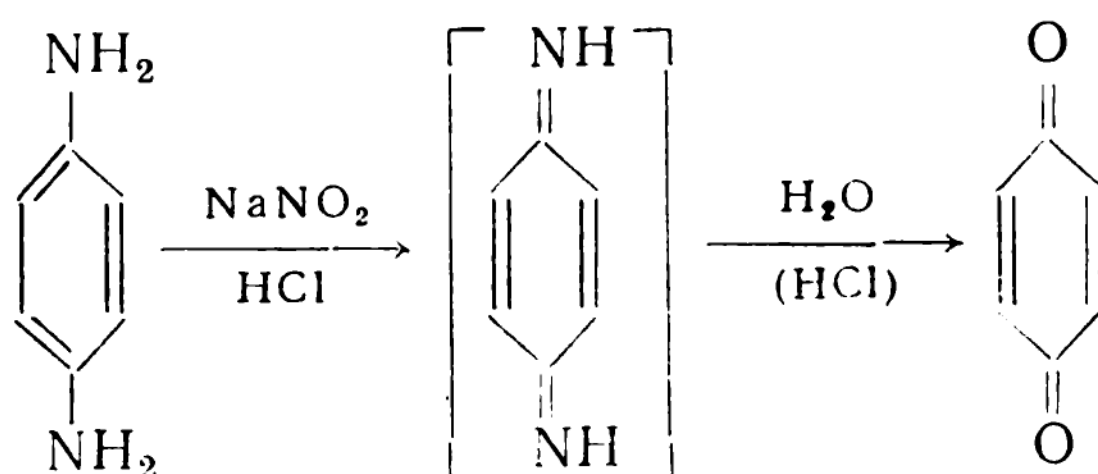


As a result of the coordinated orientation of the two amino groups, *meta*-phenylenediamine is largely prone to the azo coupling reaction with the molecule of the diazotized amine:



In order to suppress this undesirable path of the reaction it is necessary to provide a large excess of mineral acid in the reaction mixture.

Like hydroquinone, *para*-phenylenediamine is readily oxidized:



Bis-diazo compounds can be prepared from all the isomeric phenylenediamines by adding an acetic acid solution of the amine to the cooled solution of sodium nitrite in concentrated sulphuric acid.

35. The “direct” method of diazotization consists in preliminarily dissolving the amine being diazotized in a three-fold excess of mineral acid with a subsequent gradual introduction into it of a solution of an equivalent amount of sodium nitrite on cooling down to 0°C.

The “reverse” method, which is used in the diazotization of amines that are poorly soluble in aqueous solutions of mineral acids, consists in the following: a mixture of an alkaline solution of the amine being diazotized and sodium nitrite is gradually introduced into a solution of mineral acid taken in excess and cooled down to 0°C. It is usually employed in the diazotization of aminocarboxylic and aminosulphonic acids.

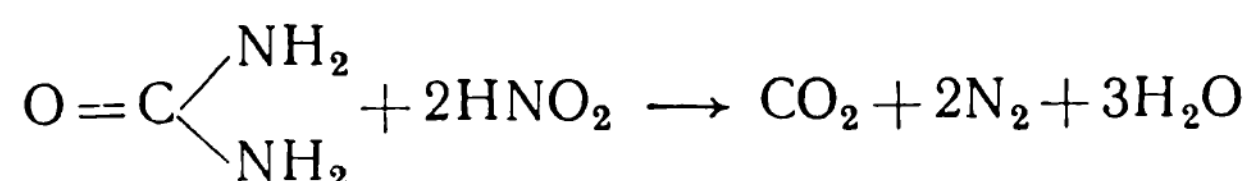
36. Apart from the “direct” (examples *b*, *c*, *g*) and “reverse” (examples *a* and *f*) methods of diazotization, for amines with a strongly decreased basicity (examples *i* and *j*) there has been developed the following method: an amine is dissolved in a mixture of concentrated phosphoric and sulphuric acids and the resulting solution is gradually added to nitrosylsulphuric acid.

On the contrary, amines of enhanced basicity that are prone to oxidation (examples *d*, *e*, and *h*) and decomposition by mineral acids are diazotized as follows: a salt of an amine is dissolved or suspended in water or in any organic solvent and is treated on cooling by such a mild nitrosating agent as alkyl or acetyl nitrite.

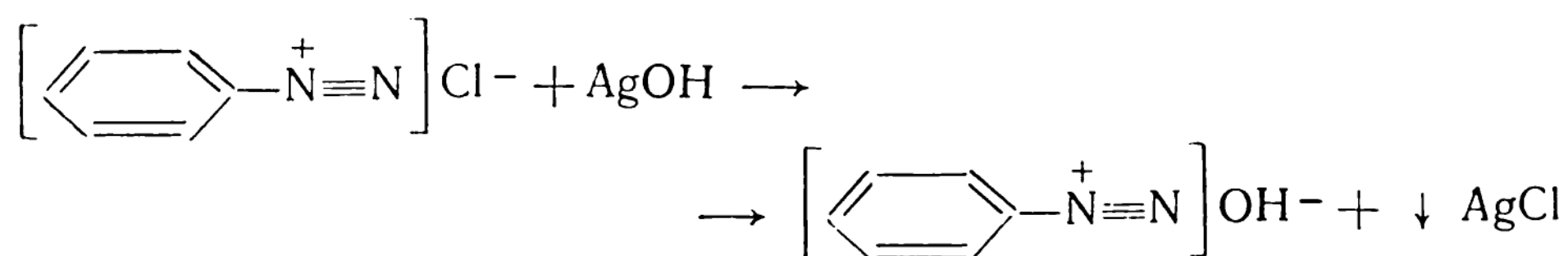
38. The termination of diazotization is determined with the aid of starch-iodide paper (paper impregnated with a solu-

tion of potassium iodide and starch). Nitrous acid is an oxidant and when contained in excess it oxidizes I^- to I^0 , which gives a characteristic colour with starch.

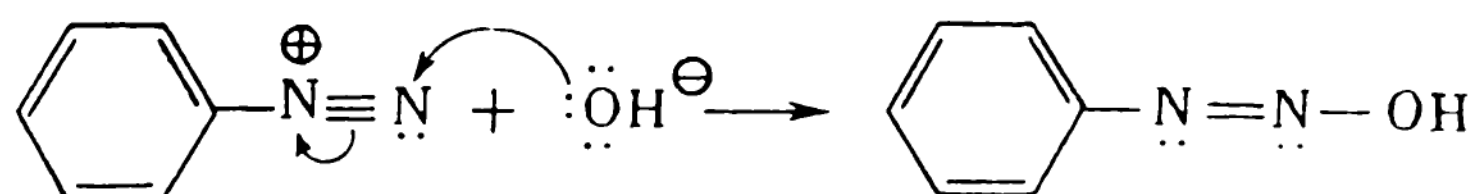
The use of an excess of nitrous acid in reactions with diazonium salts is undesirable because it may nitrosate the azo component. This reaction (nitrosation) will compete with the azo coupling reaction. The excess of nitrous acid can be removed from the reaction mixture after diazotization with the aid of dry urea which is continuously added till the evolution of gases resulting from the reaction of urea with nitrous acid is stopped:



42. When an aqueous solution of diazonium chloride is treated with an equimolecular amount of moist silver oxide, diazonium hydroxide results:

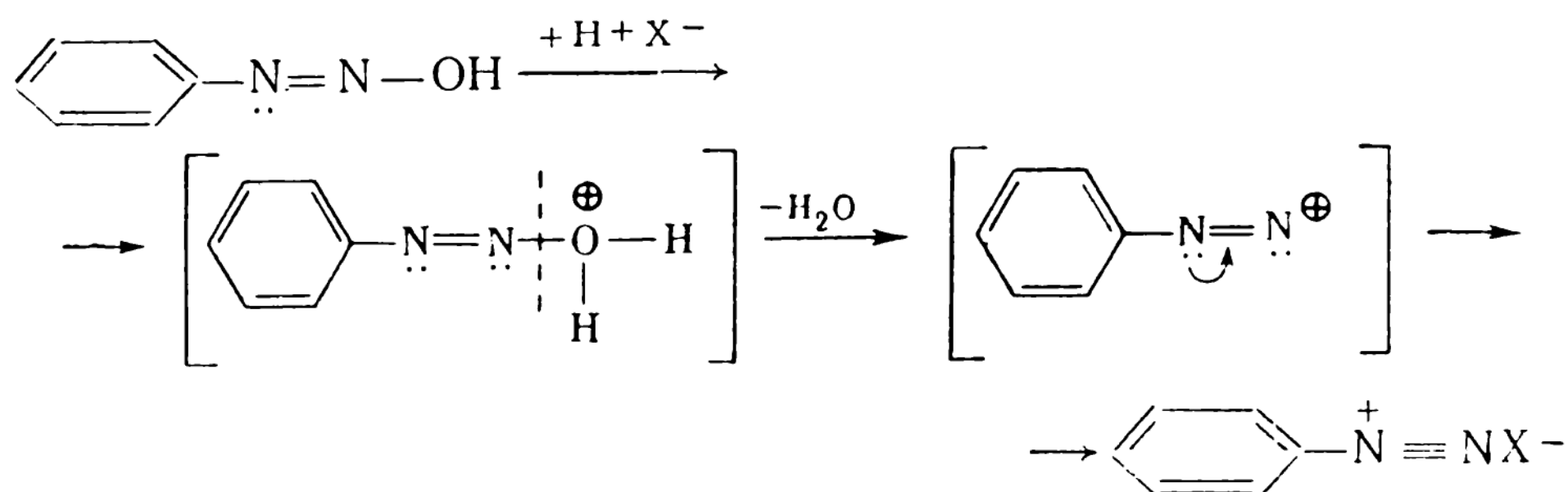


The solution becomes capable of giving a strongly alkaline reaction and conducts electricity. Its basicity and electrical conductance however fall off rapidly. This may be accounted for by the fact that the diazonium cation begins to react at a measurable rate with the hydroxyl anion acting as a nucleophile, forming a covalent bond with it:

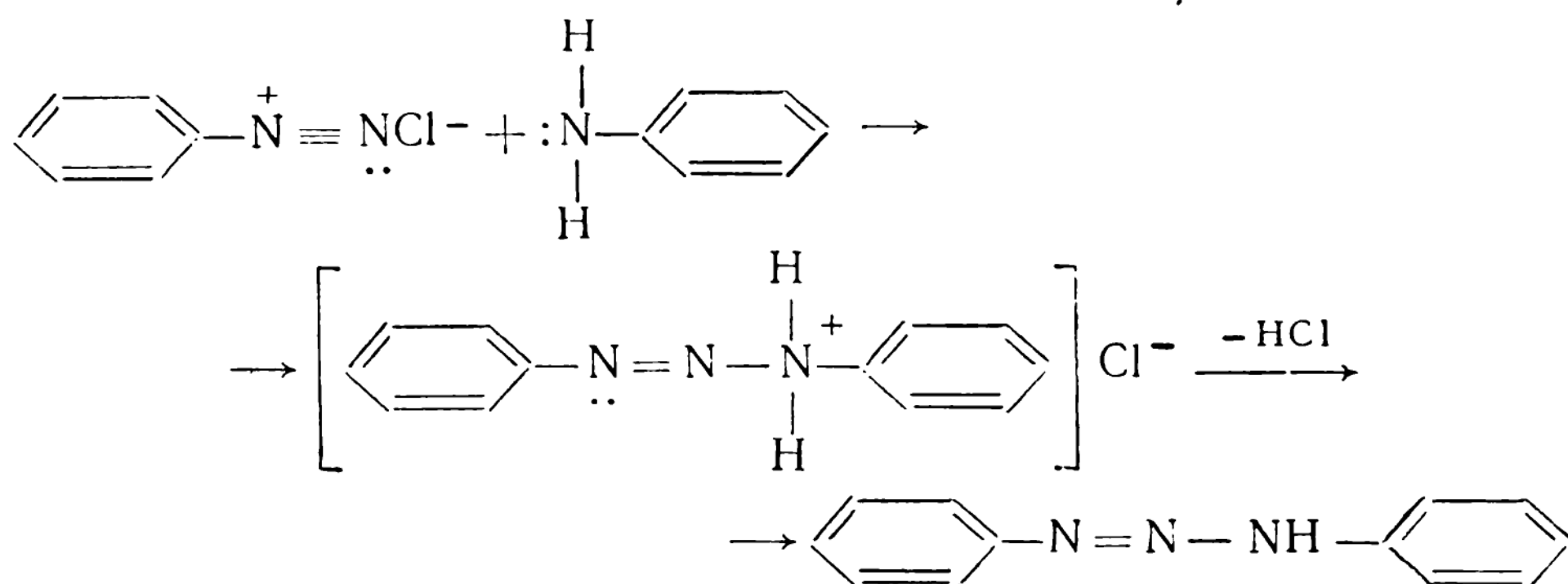


The resulting compound called diazohydrate contains no ammonium nitrogen, and the hydrogen of the hydroxyl group in it, like in phenol, is of an acidic nature. Diazohydrate is a sort of a nitrogen vinylog of phenol; when acted on by an alkali the hydrogen of the hydroxyl group is displaced by a metal, forming a diazotate: $\langle \text{benzene ring} \rangle - N = N - OMe$; but when it is

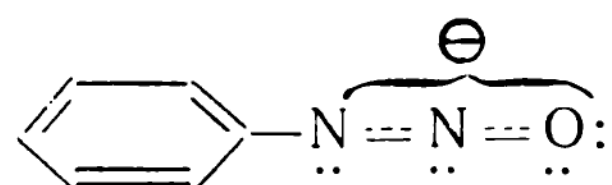
acted on by mineral acid, a diazonium salt is again formed:



43. The amount of mineral acid taken is not enough for the reaction to be carried out. Because of this, part of aniline remained in the form of a free base and reacted with the phenyldiazonium salt to give triazene:



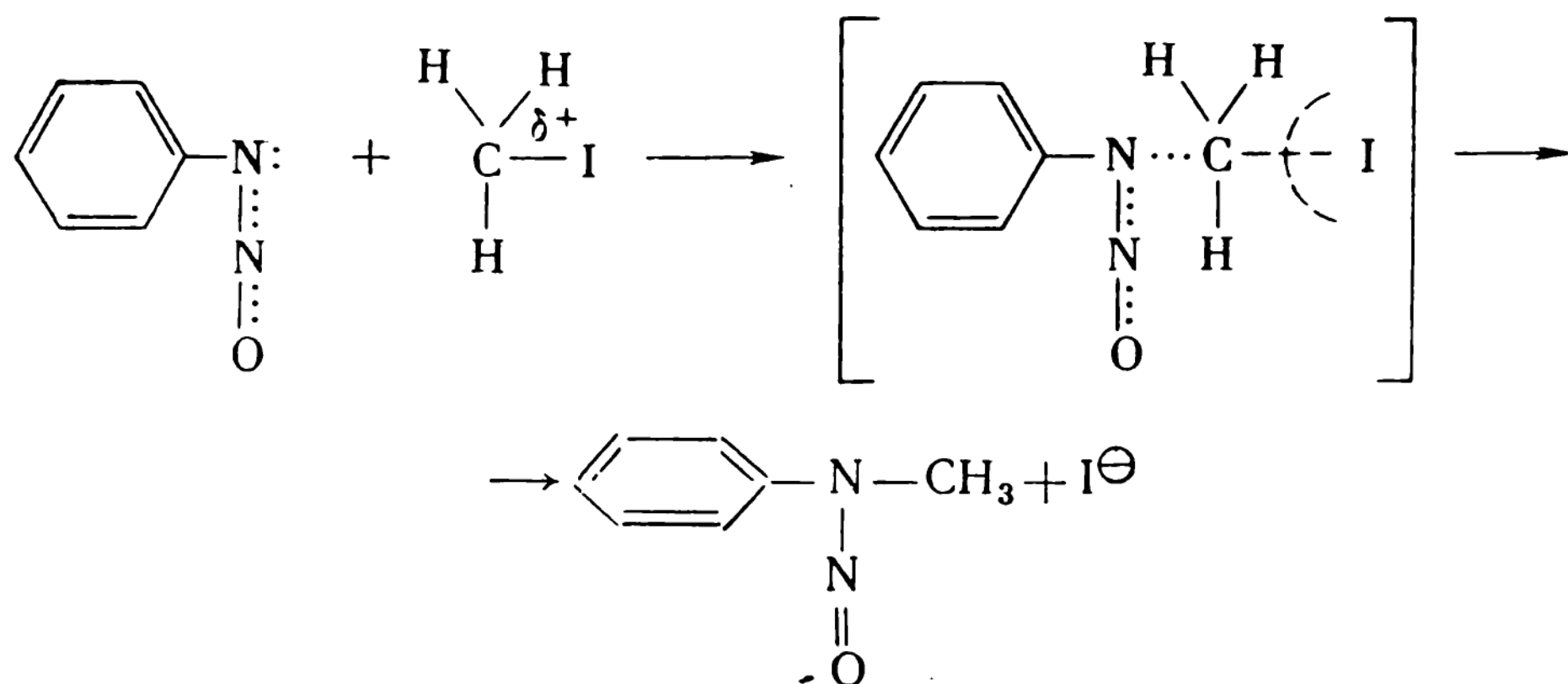
47. Diazotates of metals are salt-like products, whose anion has the following structure:



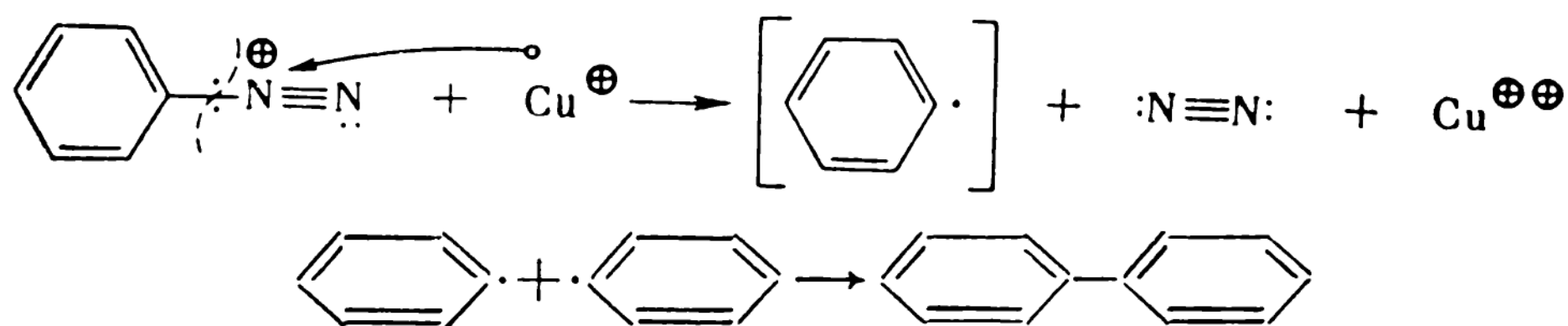
In this mesomeric anion, the major part of excess electron density is concentrated on the more electronegative oxygen atom, and the nitrogen atom attached to the benzene ring has the greatest nucleophilic reactivity.

The examples given in the problem are classed as reactions of nucleophilic displacement of the halogen in methyl iodide, which proceed according to the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms, respectively. In the first case the silver ion, being coordinated over the iodine atom, generates the carbonium ion $\text{CH}_3^\oplus$, which will react with the mesomeric anion at the site of greatest electron density—at the oxygen atom. In the second case

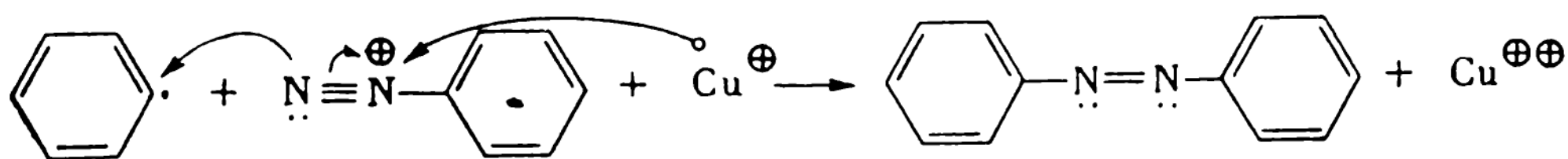
the mesomeric anion will attack the electron-deficient carbon atom in methyl iodide by one of its atoms, the one that has the highest nucleophilic reactivity, i.e., the nitrogen atom



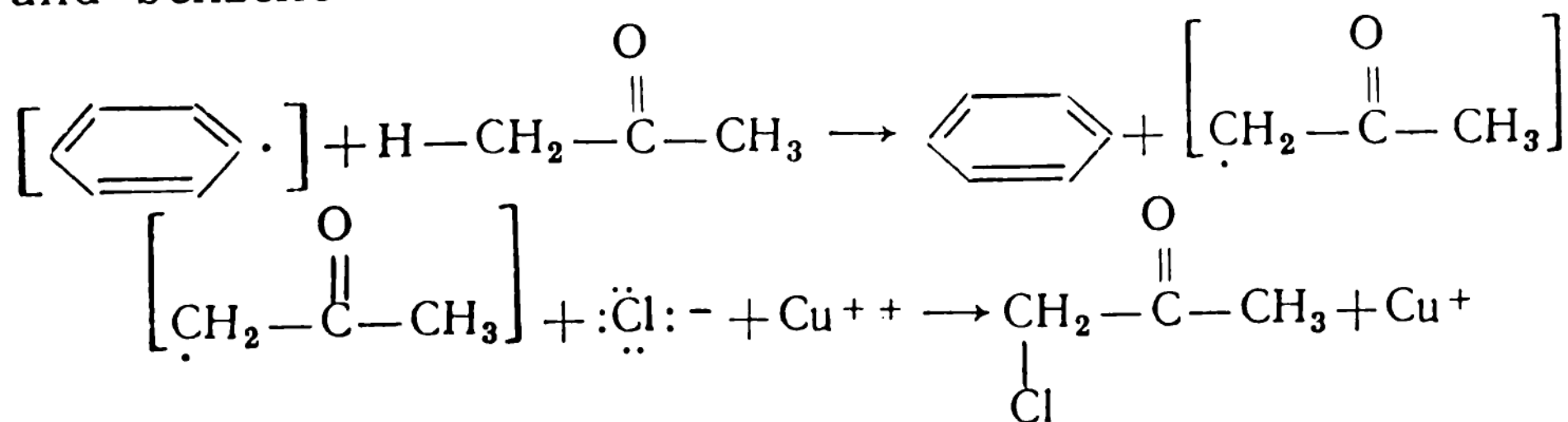
51. The recombination of two phenyl radicals involved in the reaction of displacement of the diazo group proceeding by the homolytic mechanism leads to diphenyl formed as a side product:



When the phenyl radical reacts with the diazonium cation, with univalent copper taking part in the reaction, there is formed, as a by-product, azobenzene



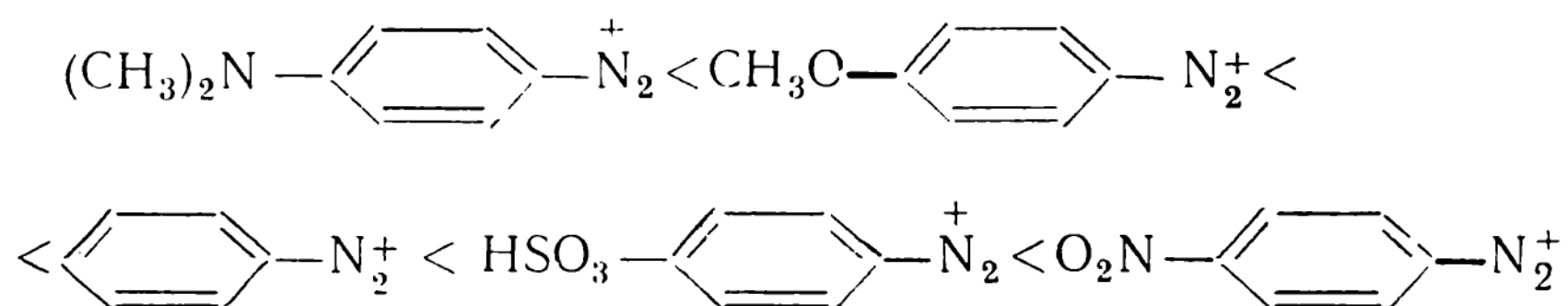
and in the presence of acetone, there are formed chloroacetone and benzene



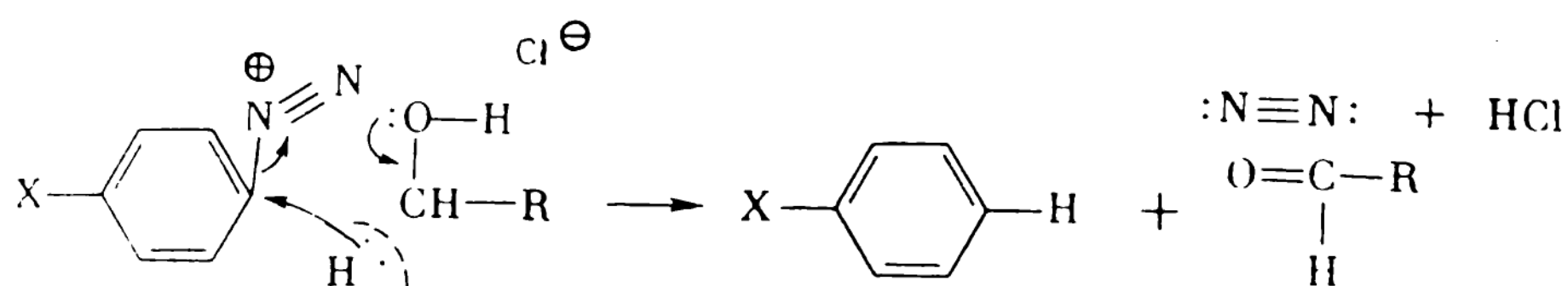
If the homolytic decomposition of the diazonium salt is carried out in the presence of nitrobenzene, 4-nitrodiphenyl is formed rather than 3-nitrodiphenyl, which must result from the attack of an electrophilic particle on the nitrobenzene molecule.

When the phenyl radical attacks the *para*-position in the nitrobenzene molecule, there is formed the most favourable transition state with a larger number of sites for distribution of an unpaired electron.

54. The ratio "displacement by OR/displacement by H" decreases, depending on the X groups in the *para*-position, in the following sequence:



This may be accounted for by the fact that the replacement of the $-\text{N}_2^+$ by the $-\text{H}$ group involves, in all probability, a six-membered transition state (the process may be either homolytic or heterolytic):



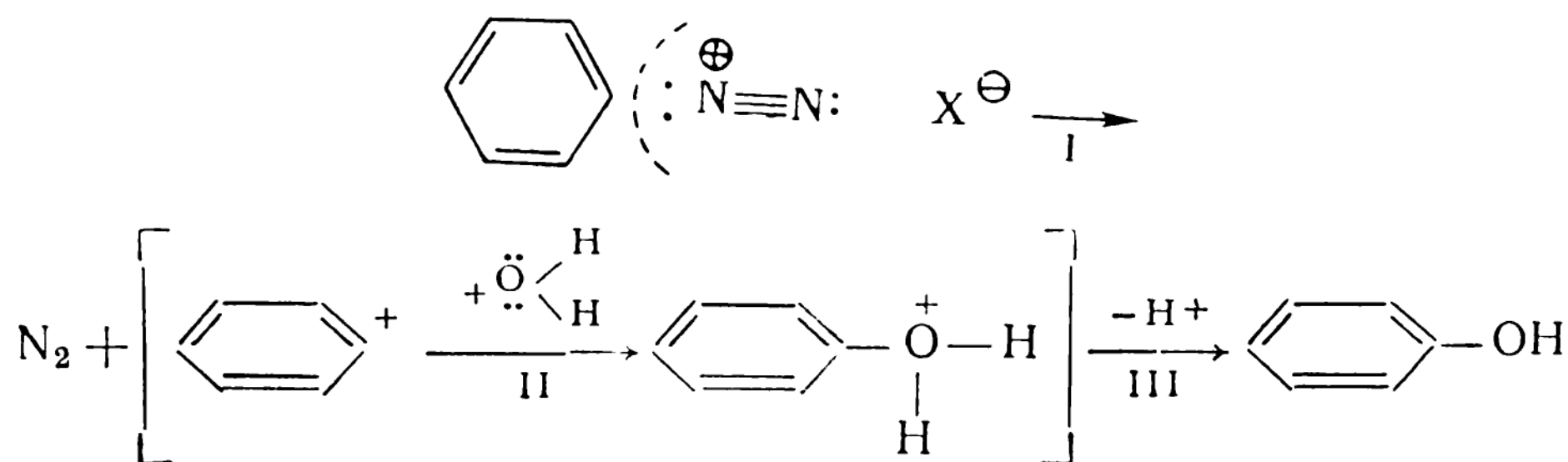
The ease of the conversion must be affected by the polarity of the carbon-nitrogen bond, which depends on the substituent X.

55. The yield of the alkoxy derivative will decrease with increasing molecular weight of the alcohol.

From methyl alcohol there is formed 93 per cent of ether, from ethyl alcohol—60 per cent, from propyl alcohol—50 per cent, and from amyl alcohol—30 per cent.

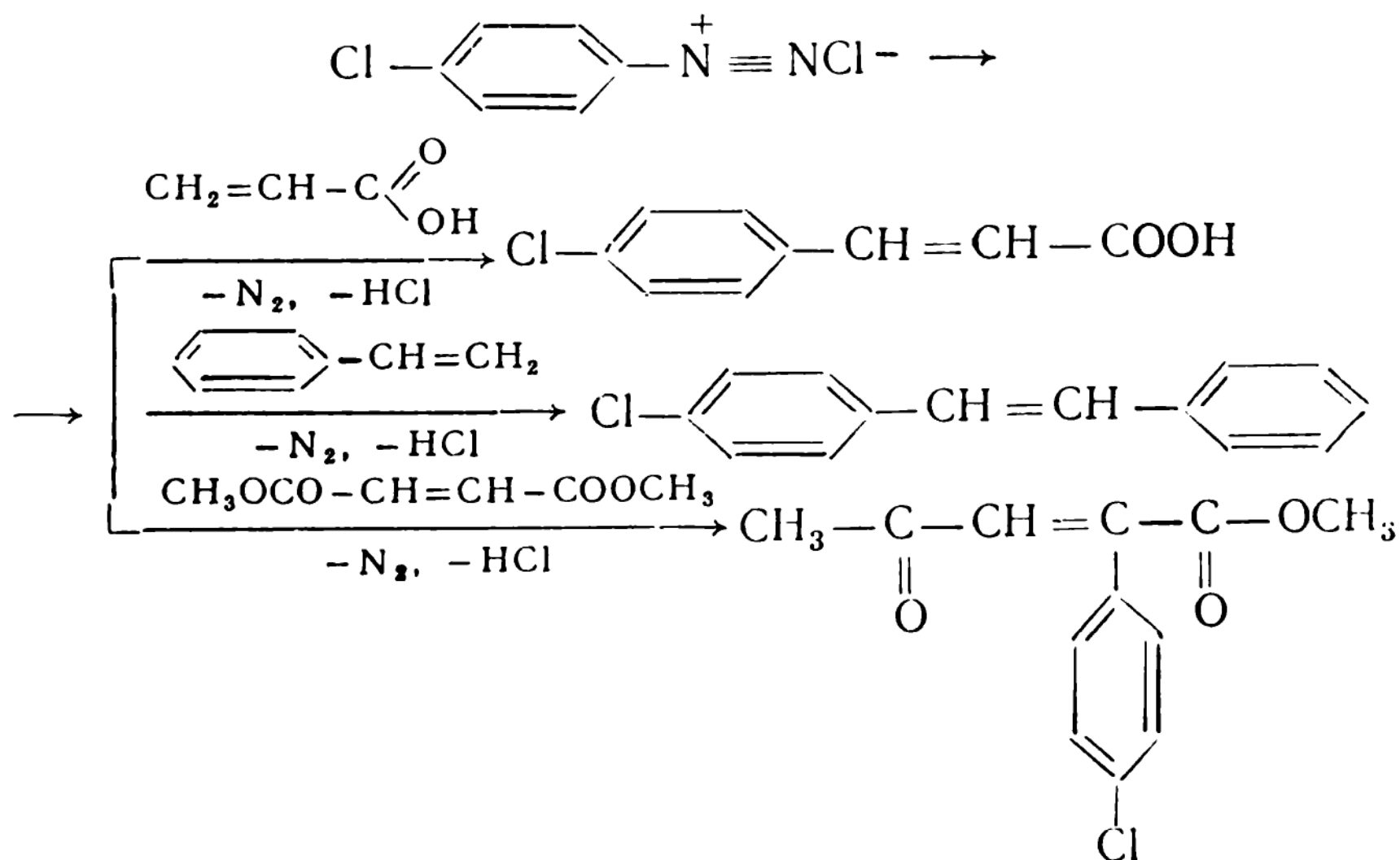
58. In the presence of even traces of moisture in the reaction space the phenyl cation is converted into phenol which is resinifiable upon thermal decomposition.

60. The formation of phenol from the phenyldiazonium salt may be visualized as follows:



At the second stage of the reaction, the anion X^- as well as the water molecule may interact in a competitive way with the phenyl cation. The greater the nucleophilic strength of the anion X^- , the more predominating will be the formation of the side product $\text{C}_6\text{H}_5\text{---}\text{X}$, apart from the phenol.

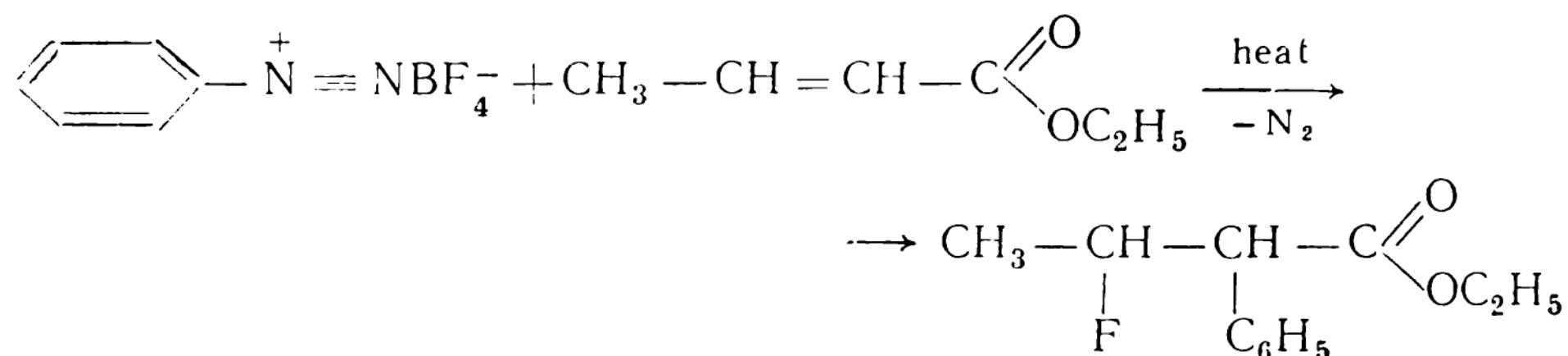
62. In the presence of cuprous salts, diazonium halides are capable of arylating compounds containing an ethylenic bond (the Meerwein condensation). For example,



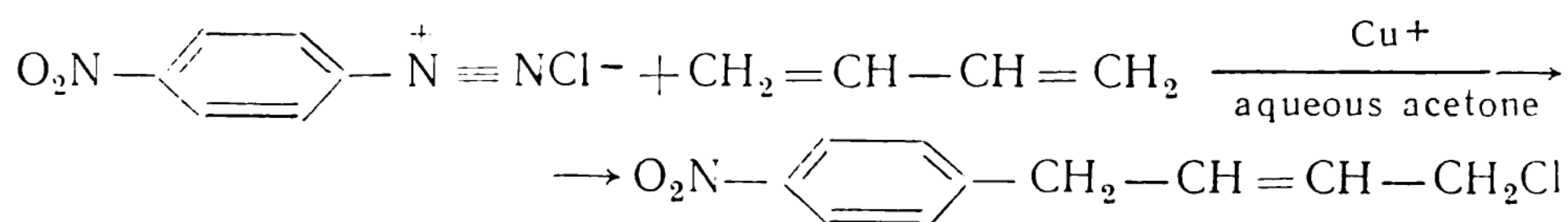
Evidently, univalent copper initiates the homolytic decomposition of the diazonium cation and the reaction is of a free-radical nature.

The thermal decomposition of boron fluorides of aryldiazonium is a heterolytic process, and in this case the addition

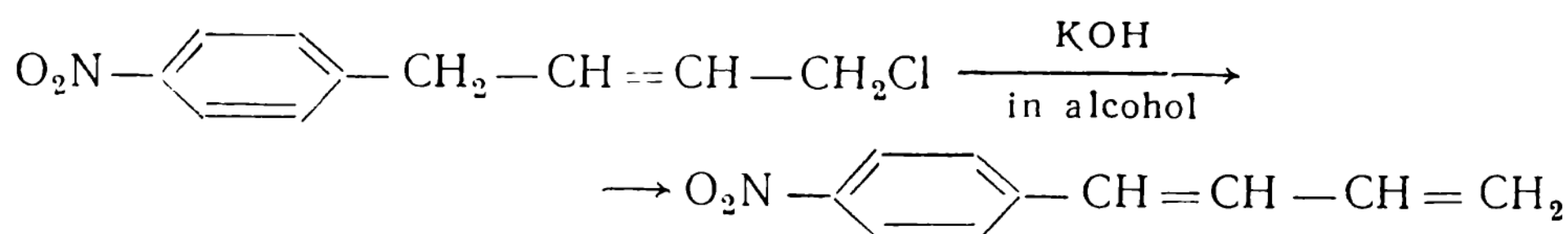
takes place in the reverse order. For instance,



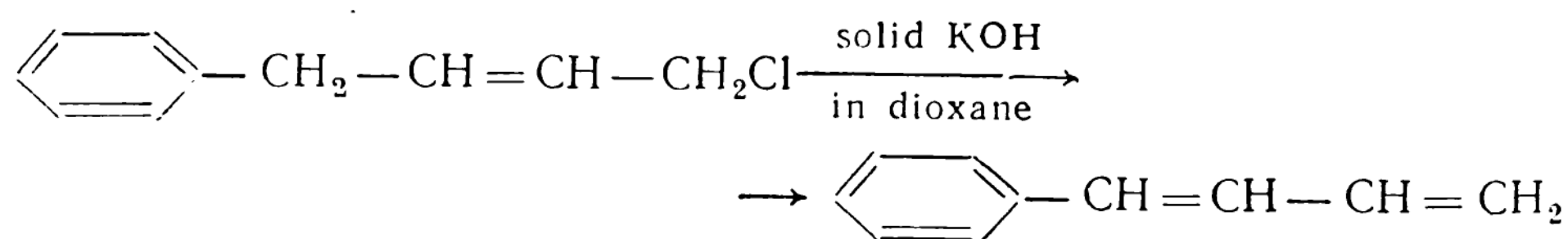
In the case of conjugated dienes the addition occurs at the 1,4-position and the corresponding halogen-arylated derivative is found to be stable



Arylbutadienes are prepared by dehydrochlorination

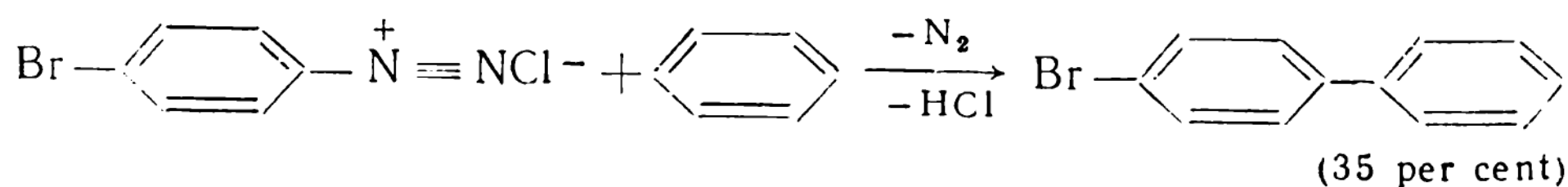


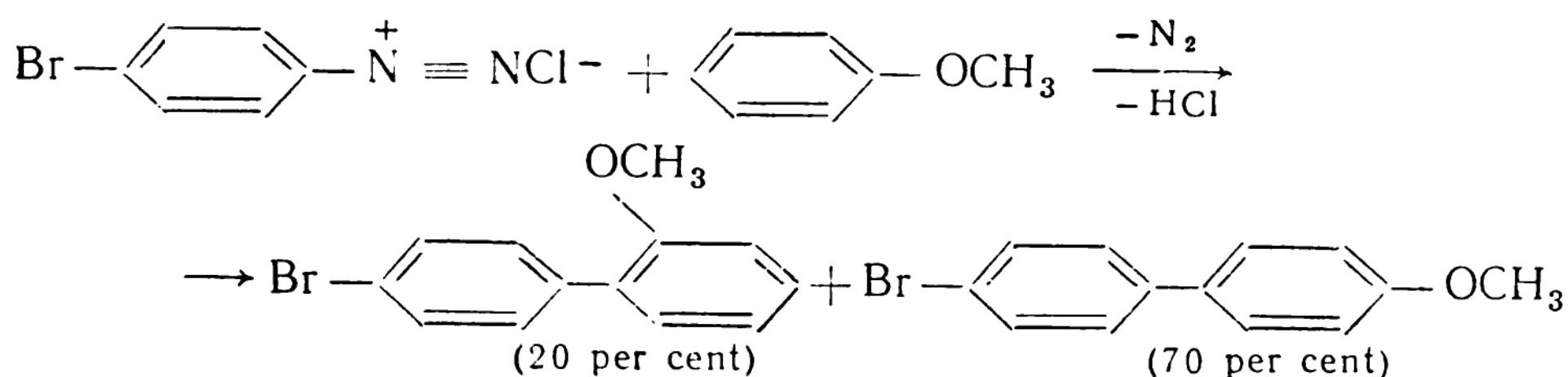
In an analogous way there can be obtained 1-phenylbuta-1,3-diene. In this case the dehydrochlorination is accomplished with the aid of solid potassium hydroxide in dioxane



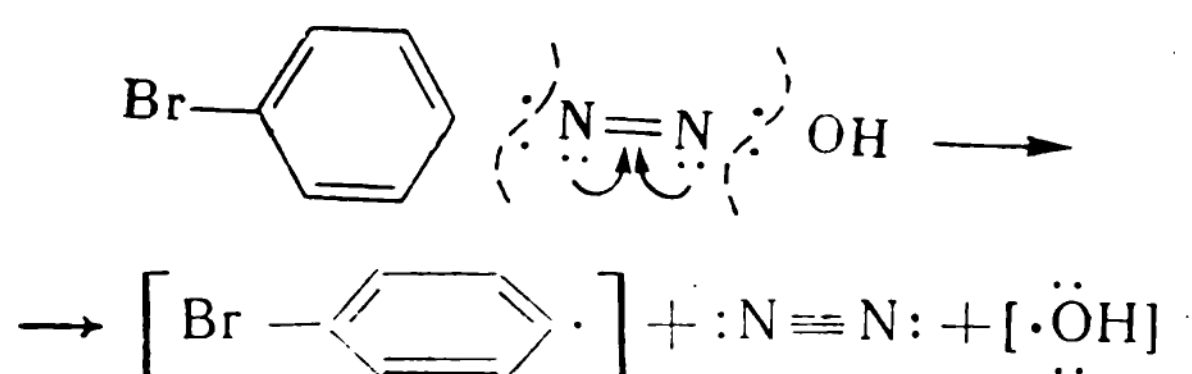
Another method of preparing diaryls, symmetrical this time, consists in gradually adding a solution of a diazonium salt to a solution of ammoniacal cuprous oxide.

64. The Gomberg method enables one to prepare unsymmetrical diphenyls. In this method, alkali is introduced into a well stirred mixture of a diazonium salt and a large excess of an aromatic compound, for example:

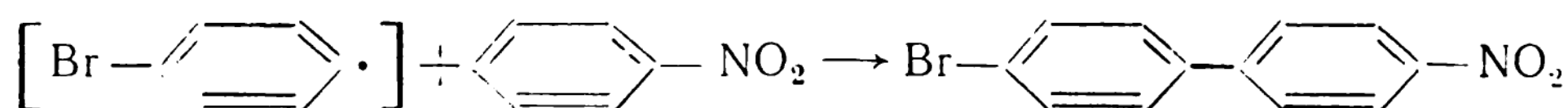




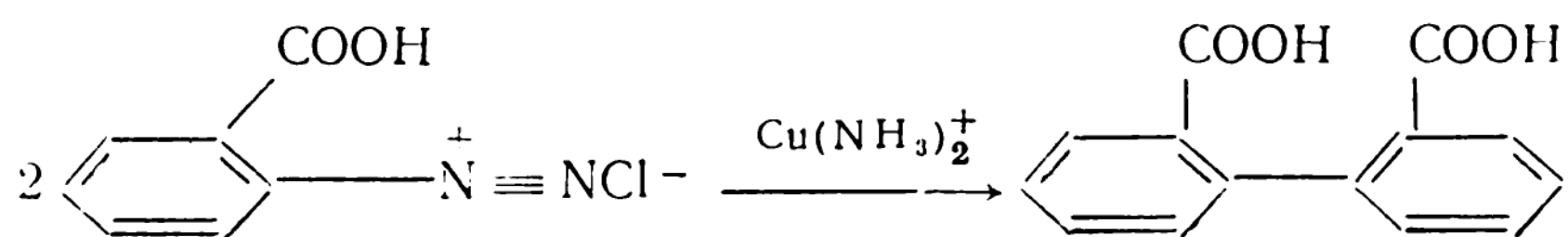
Obviously, the arylation reaction proper is preceded by the conversion of a diazonium salt into diazohydrate, which undergoes then a homolytic decomposition:



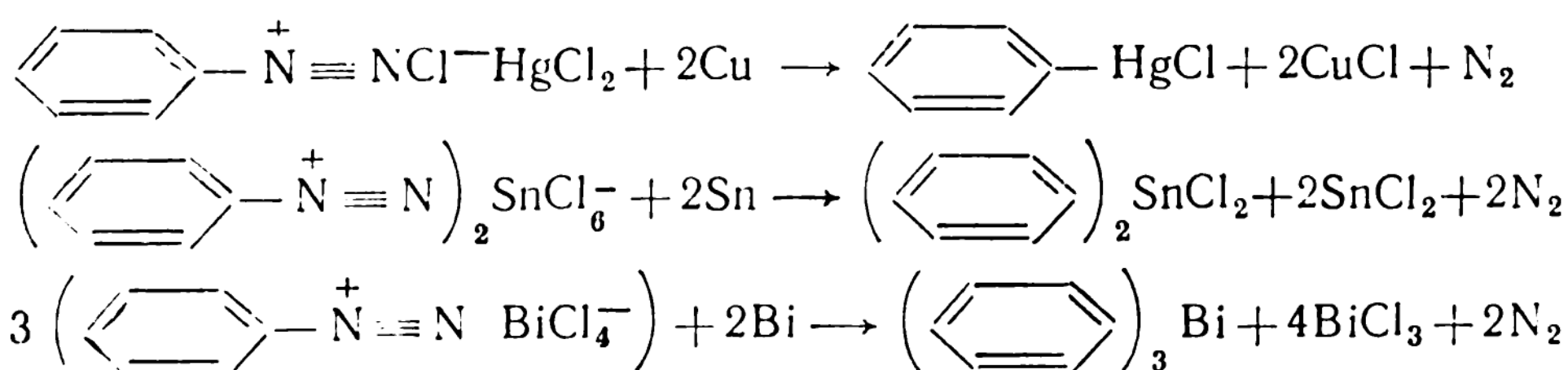
This assumption is based on the fact that if the aromatic compound used is nitrobenzene there is formed the *para*-isomer rather than the *meta*-isomer, which might have been formed if the reaction proceeded by an ionic mechanism:



Another method of preparing diaryls, symmetrical in this case, consists in the gradual addition of a solution of diazonium salt to a solution of ammoniacal cuprous oxide. This method was used to prepare, for example, diphenic acid from diazotized anthranilic acid:



66.

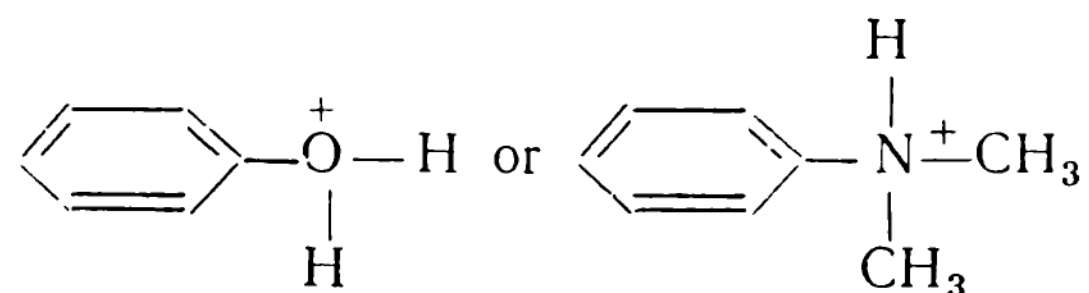


67. That the azo coupling reaction is an electrophilic substitution reaction is evidenced by the fact that the presence of electron-accepting groups increases the reactivity of diazo components.

2,4,6-Trinitrophenyldiazonium, for example, is capable of coupling even with mesitylene (1,3,5-trimethylbenzene), which does not react with many other diazonium salts.

On the contrary, electron-donating groups greatly reduce the reactivity of the diazo component. On the other hand, the electrophilic character of an azo coupling reaction is also supported by the fact that the reaction rate increases with increasing electron-donating ability (and also the number) of the substituents in the aromatic ring of the azo component. Aromatic compounds containing no strong electron-donating substituents in its nucleus cannot, as a rule, function as azo components.

69. If the pH value of the medium is lower than 5 (a strongly acidic medium), the groups of the azo component that are responsible for its enhanced reactivity may be protonated, for example:



In this case azo components lose their ability to enter into an azo coupling reaction. But if the pH value is higher than 9 (a strongly alkaline medium), from the diazo component there is formed a diazotate anion completely devoid of electrophilic properties.

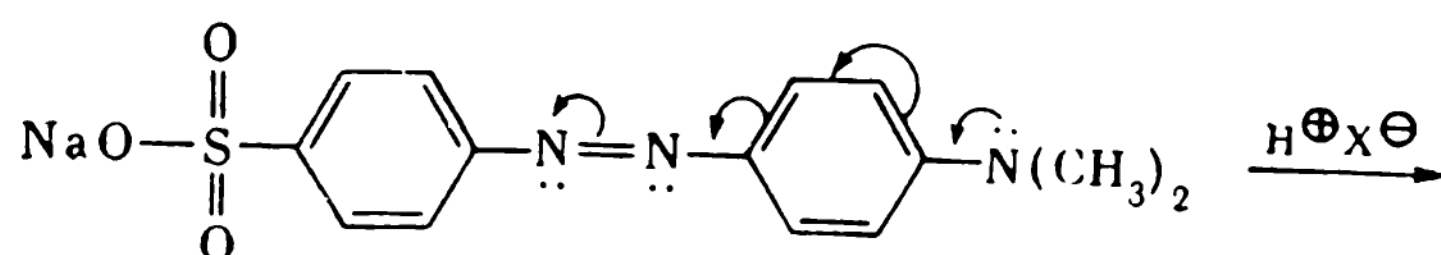
75. *Meta*-phenylenediamine, since, in contrast to the other isomers, there is observed the coordinated orientation of the amino groups in it.

77. The dimethylamino group is a very strong electron-donor; it is for this reason that *N,N*-dimethylaniline readily enters into an azo coupling reaction as the azo component. The electron-donating effect of this group on the benzene ring is fully manifested only in those cases where the *p*-orbitals of the dimethylamino group are parallel with the π -orbitals of the aromatic nucleus. Because of steric hindrances the dimethylamino group in *N,N*,2,6-tetramethylaniline is drawn

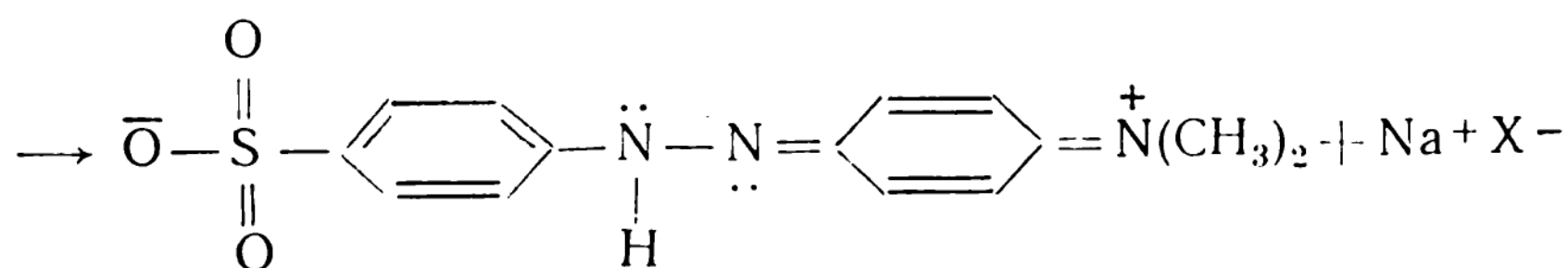
out of the plane in which it can exert a sufficiently strong effect on the benzene ring attached to it and the benzene ring loses its activity in a reaction of azo coupling.

80. Benzene is converted into nitrobenzene, which is reduced to aniline; the latter is then converted to sulphanilic acid. This acid is converted through the acid chloride to an amide, which is diazotized and couples with the *m*-phenylenediamine obtained from benzene via *m*-dinitrobenzene.

83.



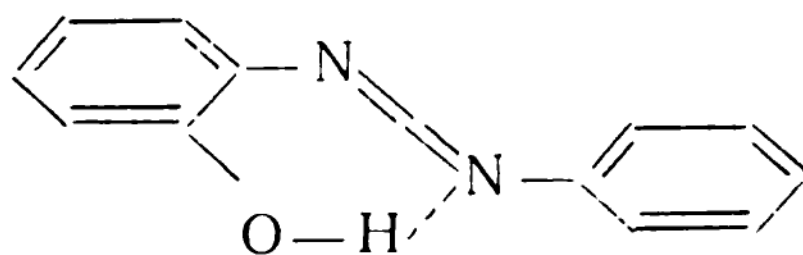
in an alkaline medium and



in an acidic medium.

The change in colour is caused by the transformation of the benzoid structure of one of the aromatic rings into the quinoid structure.

85. The difference in the properties of isomeric *o*- and *p*-hydroxyazo compounds is due to the fact that in the *ortho*-isomer there is a hydrogen bond between the hydrogen atom of the hydroxyl group and one of the nitrogen atoms of the azo group; this is explained by the following formula

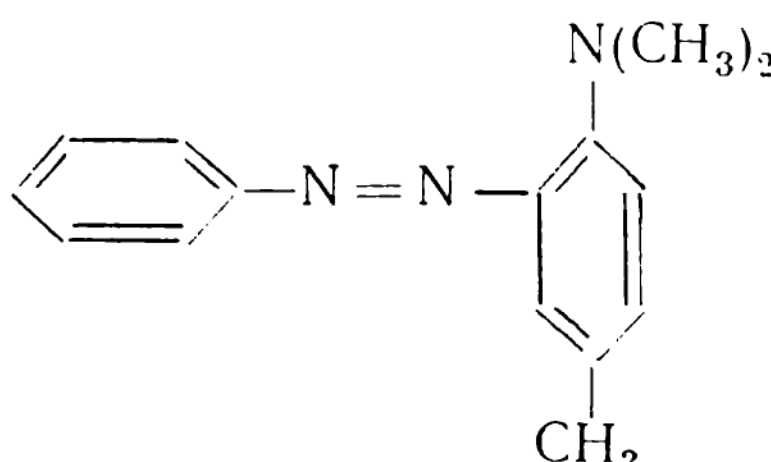
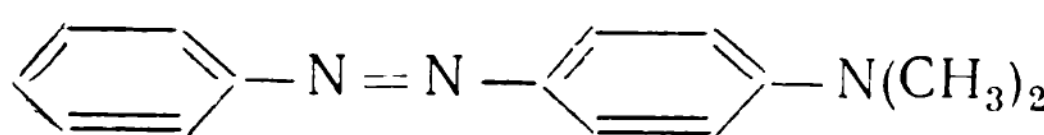
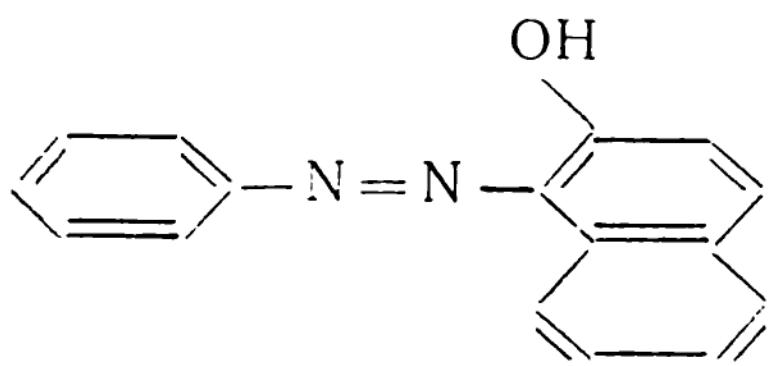
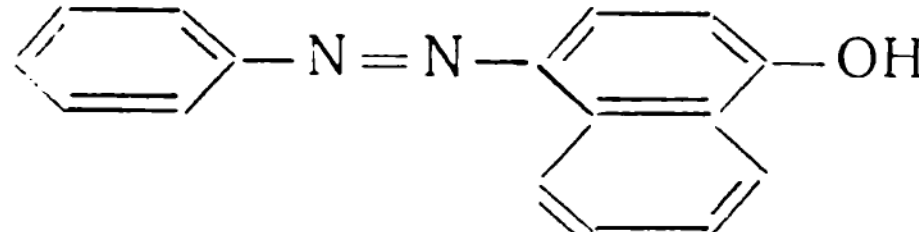
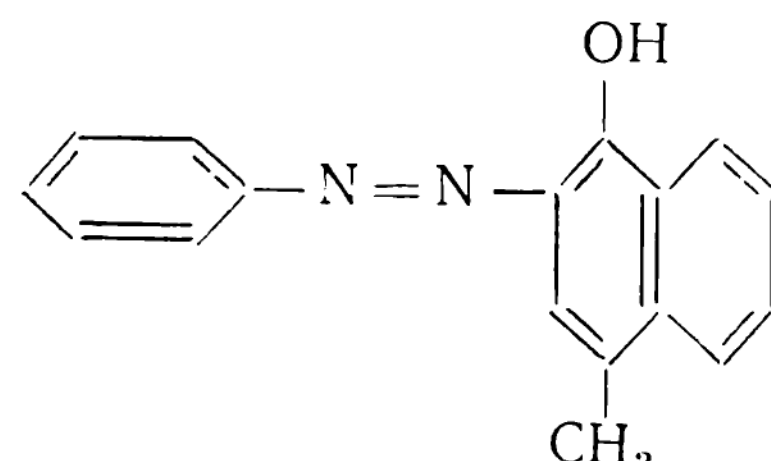


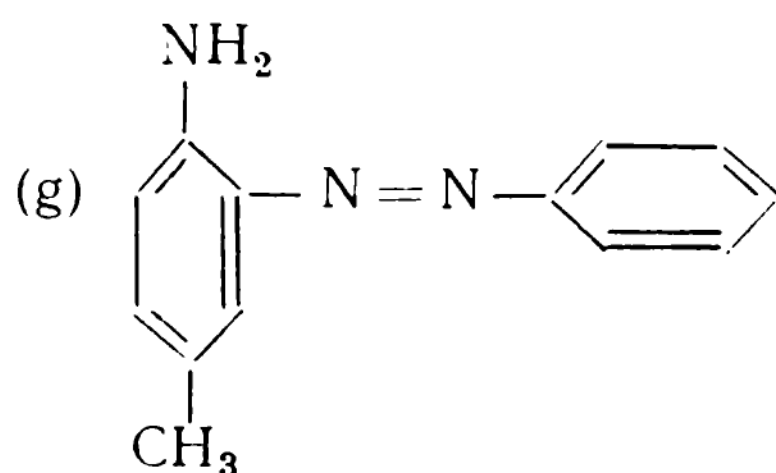
86. There are three principal methods of applying an azo dye onto the fabric:

(a) substantive dyeing, in which the dye is applied directly onto the fabric, is used only in cases where the azo dye, owing to the presence of sulpho groups, is capable of forming hydrogen bonds with the cellulose of the fabric. An example of substantive dyes is congo red.

(b) the "ice" dyeing is employed in cases where the dye is insoluble in water. In this case the fabric is impregnated with a solution of one of the components, after which it is placed in the cooled solution of the second component. An example of this type of dye is *p*-nitroaniline red.

(c) the mordant dyeing is used when the dye is capable of forming water-insoluble chelate salts with the cations of metals such as aluminium, iron(III), copper, and chromium. The fabric is soaked in solutions of salts or hydroxides of the corresponding metals (mordants) and then the dye is applied. The insoluble substances in the dye which are deposited on the fibre are called varnishes. An example of mordant dyes is β -naphthol orange containing a hydroxyl group in the *ortho*-position to the azo group.

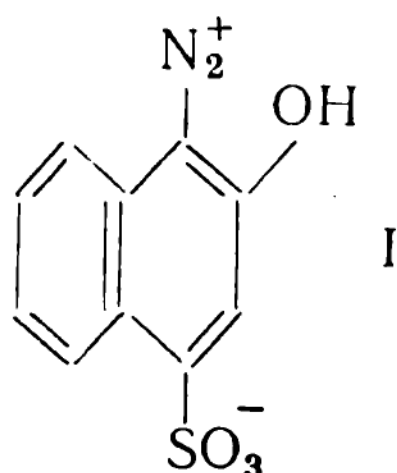
90. a)  the coupling takes place *ortho* to dimethylamino group (pH = 5);
- (b)  the carboxylic group is eliminated (pH = 8 to 9);
- (c)  the sulpho group is eliminated (pH = 8 to 9);
- (d)  the coupling takes place in the position 4 (pH = 9);
- (e) no coupling takes place;
- (f)  the coupling occurs in the position 2 (pH = 9);



the coupling is carried out at pH=5.

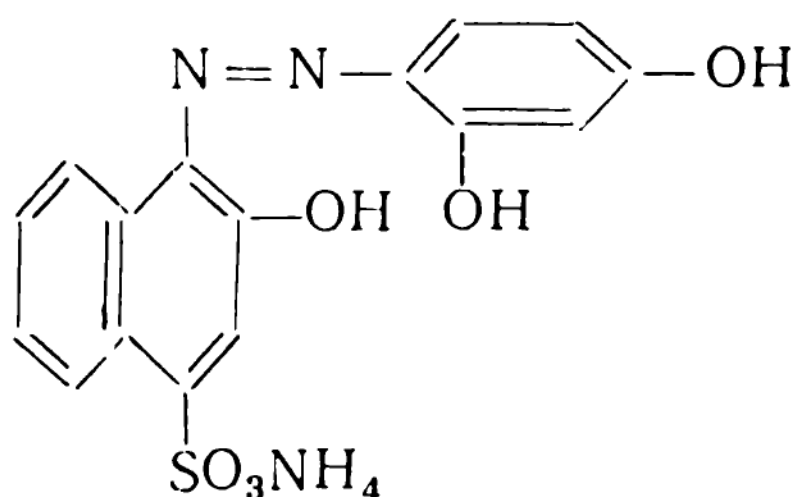
93. This is a method of reproducing drawings and written material that makes use of the azo coupling reaction.

The paper used for producing duplicates is first impregnated with a solution containing a diazo compound (for example, I), resorcinol and tartaric (or citric) acid.



In the presence of the latter, quinonediazide does not enter into the azo coupling reaction with resorcinol.

When exposed to light quinonediazide decomposes with the evolution of nitrogen only on the illuminated portions of the paper. If after this the paper is introduced into the atmosphere of ammonia which neutralizes the acid, on the unilluminated part of the paper there will take place an azo coupling reaction with the formation of a coloured azo dye.



94. (a) Benzene is successively nitrated and reduced by zinc in an alkaline solution to synthesize hydrazobenzene, which is then converted to benzidine by the action of sulphuric acid. The resulting benzidine is subjected to a diazo reaction to prepare 4,4'-diiododiphenyl.

(b) Benzene is successively nitrated and reduced to synthesize aniline. Aniline sulphate is heated at 180°C to give sulpha-

nilic acid. The latter is brominated and the sulpho group in the resulting 2,6-dibromide is subjected to elimination (in an acidic medium, superheated steam). The thus obtained 2,6-dibromoaniline is converted by a diazo reaction to 1,2,3-tribromobenzene.

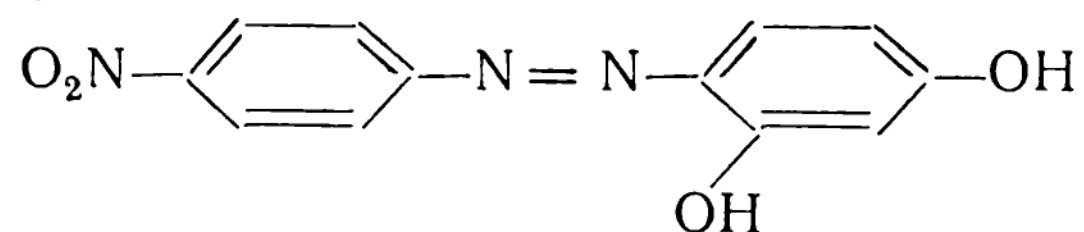
(f) From benzene there are obtained nitrobenzene and aniline (see 94b). The latter is diazotized and sodium borofluoride is added to the phenyldiazonium chloride obtained. The precipitated phenyldiazonium borofluoride is dried (see answer 58) and then subjected to thermal decomposition in the presence of nitrobenzene.

95. In all the cases aniline is first prepared (see 94b), and then acetic anhydride and acetanilide. The last-named compound is nitrated and the acetyl group is then eliminated (through hydrolysis) to synthesize *p*-nitroaniline.

(a) *p*-Nitrophenylhydrazine is prepared by diazotization of *p*-nitroaniline and by reduction of the resulting diazo compound (see Problem 115).

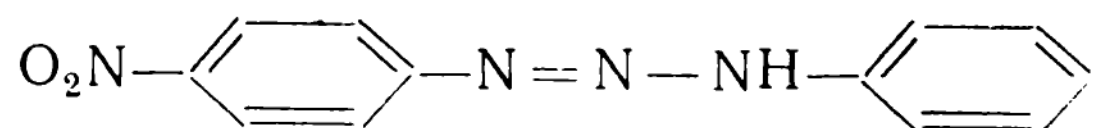
(b) *p*-Dinitrobenzene is synthesized from diazotized *p*-nitroaniline (see 94a) by decomposition in a concentrated solution of sodium nitrite in the presence of molecular copper.

(c) Magneson-1 is prepared by the azo coupling of the diazotized *p*-nitroaniline with resorcinol. The latter is obtained by the alkaline fusion of the sodium salt of benzene-*m*-disulpho acid, which is synthesized by sulphonation of benzene with oleum on heating. The structure of magneson-1 is as follows:



(d) Cadion is synthesized by the reaction of aniline (see Problem b) and diazotized *p*-nitroaniline (see Problem 95a) in an acetate buffer solution.

The structure of cadion is:



(e) From *p*-nitroaniline (see Problem 95a) by iodination there is prepared 2,6-diiodo-4-nitroaniline; the amino group in the resulting compound is replaced through a diazo reaction by I.

(f) The amino group in diazotized *p*-nitroaniline (see Problem 95a) is displaced by a cyano group. Then *p*-nitrobenzonitrile is reduced to *p*-aminobenzonitrile. The amino group in the latter is replaced (through a diazo reaction) by a cyano group. The thus synthesized dinitrile is subjected to hydrolysis.

(g) *p*-Nitrobenzonitrile (see Problem 95f) is hydrolysed by concentrated sulphuric acid.

96. (d) From benzene there is obtained *m*-dinitrobenzene and then, by partial reduction of the latter, *m*-nitroaniline (see 29a). The bromination of *m*-nitroaniline leads to 2,4,6-tribromo-3-nitroaniline. The amino group in the latter is replaced through diazo reaction by bromine, following which the nitro group is reduced to the amino group and again bromine is substituted for the amino group by diazo reaction.

98. (c) Aniline is prepared from benzene (see Problem 94b), and then tribromoaniline. The amino group in the last-named compound is displaced by fluorine (the Schiemann reaction, see Problem 58).

101. (c) From *m*-nitroaniline (see 96d) there is obtained by diazo reaction *m*-nitroanisole (see 54, 55); the latter is reduced with zinc and alkali (see 29) to 3,3'-dimethoxyhydrazobenzene, which is converted by treatment with sulphuric acid (see Problem 14 for the benzidine rearrangement) to 2,2'-dimethoxybenzidine. The elimination of both amino groups in the resulting compound (see 54) leads to 2,2'-dimethoxydiphenyl.

102. (a) The aniline prepared from benzene (see 94b) is converted by diazo reaction first to benzonitrile and then to benzoic acid (hydrolysis). The last-named compound is nitrated and the *m*-nitrobenzoic acid obtained is reduced to *m*-aminobenzoic acid, which is converted by diazo reaction to *m*-hydroxybenzoic acid. Then the methylation with methyl iodide (prepared from methyl alcohol) in alkaline medium leads to methyl *m*-methoxybenzoate; the alkaline hydrolysis of this ester results in the formation of *m*-methoxybenzoic acid.

103. (b) Toluene is converted by nitration and subsequent reduction of the nitro group to *p*-toluidine, and then by diazo reaction to *p*-iodotoluene. The last-named compound is oxidized to synthesize *p*-iodobenzoic acid; this acid is brominated to give 3-bromo-4-iodobenzoic acid.

(c) *p*-Fluorotoluene is made by the Schiemann reaction (see Problem 58) from *p*-toluidine (see 103b).

(d) The diazo reaction of *p*-toluidine (see 103b) leads to *p*-cresol, which is subjected to iodination to synthesize 3,5-diiodo-*p*-cresol.

(e) *p*-Toluidine (see 103b) is brominated and the amino group is eliminated by diazo reaction (see 54).

104. (a) *p*-Toluidine (see 103b) is acylated with acetic anhydride prepared from acetic acid and then nitrated. The hydrolysis of the resulting 3-nitro-4-acetylamino-toluene gives 3-nitro-4-aminotoluene. The amino group of this compound is eliminated by diazo reaction (see 54) to synthesize *m*-nitrotoluene, which is converted by reduction to *m*-toluidine.

(b) 3,3'-Ditolyl is made from *p*-toluidine (see 104a) in just the same way as other symmetrical diaryls (see 64).

(c) *m*-Toluidine is acylated with acetic anhydride (prepared from acetic acid) and the methyl group is oxidized to the carboxyl group. The resulting *m*-acetylamino-benzoic acid is converted by hydrolysis to *m*-aminobenzoic acid, which is converted through diazo reaction to *m*-iodobenzoic acid.

(d) *m*-Toluic acid is made from *m*-toluidine (see 104a), the amino group is replaced by a nitrile group (diazo reaction) and then the nitrile group is hydrolysed (with concentrated sulphuric acid) to a carboxyl group.

105. (c) Nitrobenzene is reduced to aniline, from which there is made 2,4,6-tribromoaniline. In the latter the amino group is replaced by fluorine according to the Schiemann mechanism (see 58).

(d) Nitrobenzene is brominated to give *m*-bromonitrobenzene, which is then reduced to *m*-bromoaniline (see 29h). The last-named compound is subjected to diazo reaction to give *m*-bromophenol.

108. The reaction of phthalic anhydride with ammonia gives phthalimide, which is subjected to the Hofmann rearrangement. The anthranilic acid thus obtained is diazotized (see 35) and brought into azo coupling reaction with dimethylaniline made from benzene, methyl iodide and inorganic reagents (benzene is nitrated, nitrobenzene is reduced, and aniline is methylated).

109. *m*-Dinitrobenzene prepared by nitration of benzene is subjected to partial reduction (see 29a). Then phenol is syn-

thesized, from which salicylic acid is made by the Kolbe reaction. The sodium salt of this acid is brought into coupling reaction with a diazonium salt prepared from *m*-nitroaniline.

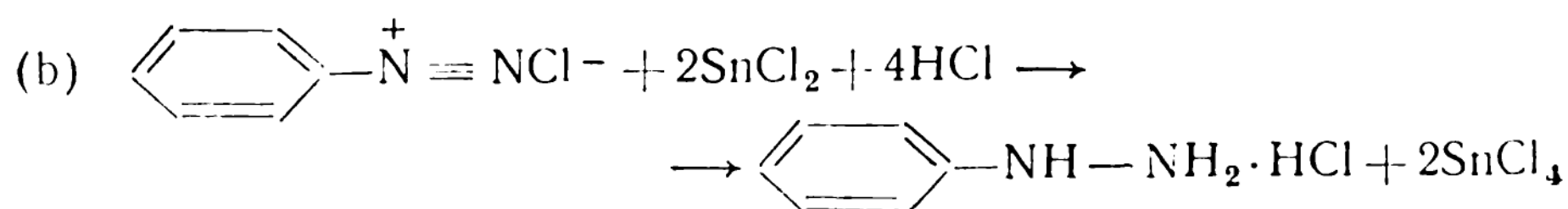
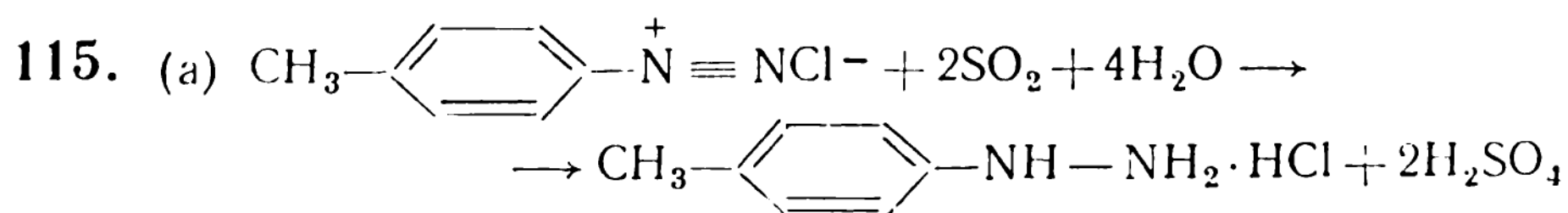
110. *p*-Nitrophenol is reduced with sodium sulphide to *p*-aminophenol, and phenyldiazonium chloride is made from aniline. The azo coupling reaction carried out at pH=9 gives 2-phenylazo-4-aminophenol, which is reduced with sodium hydrosulphite in alkaline medium to give 2,4-diaminophenol. The azo coupling of the same components at pH=5 yields 3-phenylazo-4-aminophenol, from which 3,4-diaminophenol is synthesized by the above-described method through the reductive cleavage of the azo group.

111. Ethyl alcohol is used to synthesize buta-1,3-diene (see the Lebedev reaction in textbooks), and from *p*-nitroaniline there is synthesized the corresponding diazonium chloride. The interaction of these reagents yields 1-(*p*-nitrophenyl)-buta-1,3-diene (see 62).

112. The condensation of acetone in the presence of concentrated sulphuric acid leads to mesitylene (1,3,5-trimethylbenzene), and benzene is used to accomplish the following conversions: benzenesulphoacid → phenol → picric acid → picryl chloride → picramide. Then picramide is diazotized (see 36) and is brought into azo coupling reaction with mesitylene (see 67).

113. By reducing nitrobenzene with zinc in an aqueous solution of alkali one obtains a symmetrical diphenylhydrazine —hydrazobenzene.

To synthesize an unsymmetrical diphenylhydrazine, nitrobenzene is first reduced to aniline and its hydrochloride is converted by heating to diphenylamine. Then diphenylamine is nitrosated and the nitroso derivative is reduced.



CHAPTER 9

SYNTHESIS AND PROPERTIES OF HETEROCYCLIC COMPOUNDS

INTRODUCTION

Problems and exercises dealing with the topic "heterocyclic compounds" cover mainly the most important five- and six-membered heterocycles included in a course of organic chemistry.

This topic is subdivided into two parts: the first includes theoretical questions concerning the general properties and the principal reactions of furan, pyrrole, thiophene, pyridine, quinoline, and some of their derivatives. The second is devoted to synthesis and conversions of heterocyclic systems.

The systematization of the material within each section is based on the size of the cycle.

The section devoted to preparative syntheses ends with exercises in the preparation and properties of some of the most important heterocycles with two heteroatoms, which find practical application (medicines, analytical reagents). The problems of the aromaticity of heterocyclic systems (their stability, the tendency to take part in electrophilic substitution reactions, and the effect on the groupings attached to them) are also dealt with in this chapter.

To solve synthetic problems it is necessary to know not only the simplest and most important methods of preparing heterocycles (synthesis via 1,4-dicarbonyl compounds, the Fischer, Skraup, and Doebner-Miller syntheses) but also certain conversions typical of them. Great attention is paid to the synthesis of starting materials, which makes it possible to remind of the most important synthetic methods for preparing aliphatic and aromatic compounds discussed in the previous chapters. Answers are given to all questions.

Problems and Exercises

1. GENERAL PROPERTIES AND REACTIONS OF HETEROCYCLES

1. How many isomers can there exist for furan derivatives containing two identical and two different substituents?

2. Explain why pyridine exhibits basic properties and pyrrole does not.

3. How could you account for the difference in the resistance of pyrrole and pyridine rings to the action of acids?

4. How can you explain the instability of furan and pyrrole against the action of acidic agents?

5. What does one imply when speaking of the "superaromatic" properties of furan and pyrrole?

6. What compounds of the benzene series can furan and pyrrole be compared with from the viewpoint of their ability to enter into electrophilic substitution reactions?

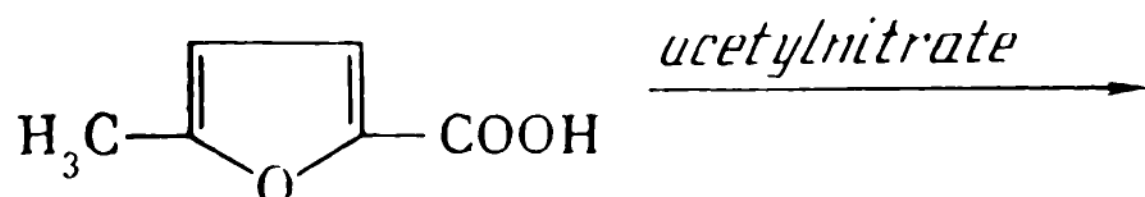
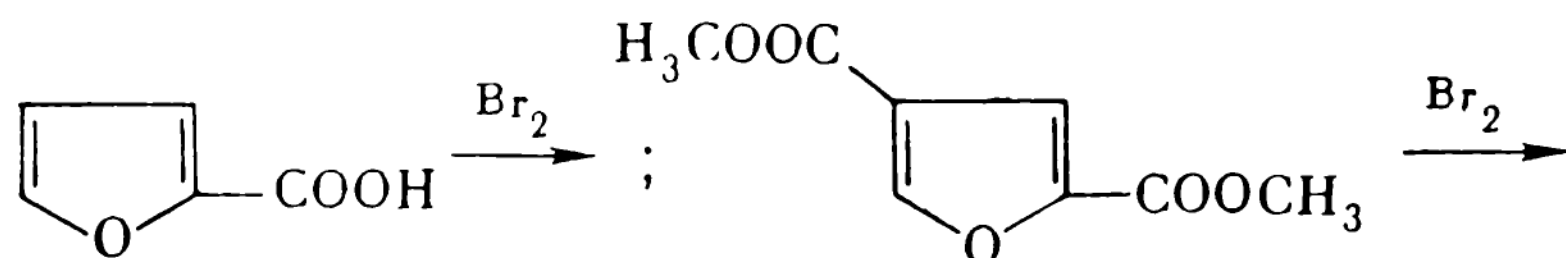
7. Which of the following heterocyclic compounds—furan, thiophene or pyrrole—resembles benzene more closely with respect to stability?

8. Arrange thiophene, pyrrole, furan, and benzene in order of increasing reactivity in electrophilic substitution reactions.

9. How can you account for the high reactivity of the α -positions in the nuclei of thiophene, furan, and pyrrole as compared with β -positions?

10. Arrange the following compounds in order of increasing ease of electrophilic substitution in the nucleus: pyrrole, benzene, thiophene, toluene, furan, mesitylene, phenol, aniline.

11. Into what position will a substituent enter in the following substitution reactions in the furan series:



12. Suggest methods for separating benzene from thiophene with and without recovery of the components.

13. The interaction of furan with maleic anhydride and with mesityl oxide proceeds according to different schemes. Write the schemes of both reactions.

14. How does pyrrole react with maleic anhydride?

15. Name reactions that proceed according to the same scheme for sodium phenolate and pyrrolpotassium.

16. How could you separate a mixture of thiophene and sylvan (α -methylfuran) without resort to distillation (each of the components must be separated in an individual state)?

17. What compound of the benzene series resembles pyridine most closely in its attitude to electrophilic reagents?

18. Give examples of three different reactions of nucleophilic substitution in the pyridine nucleus.

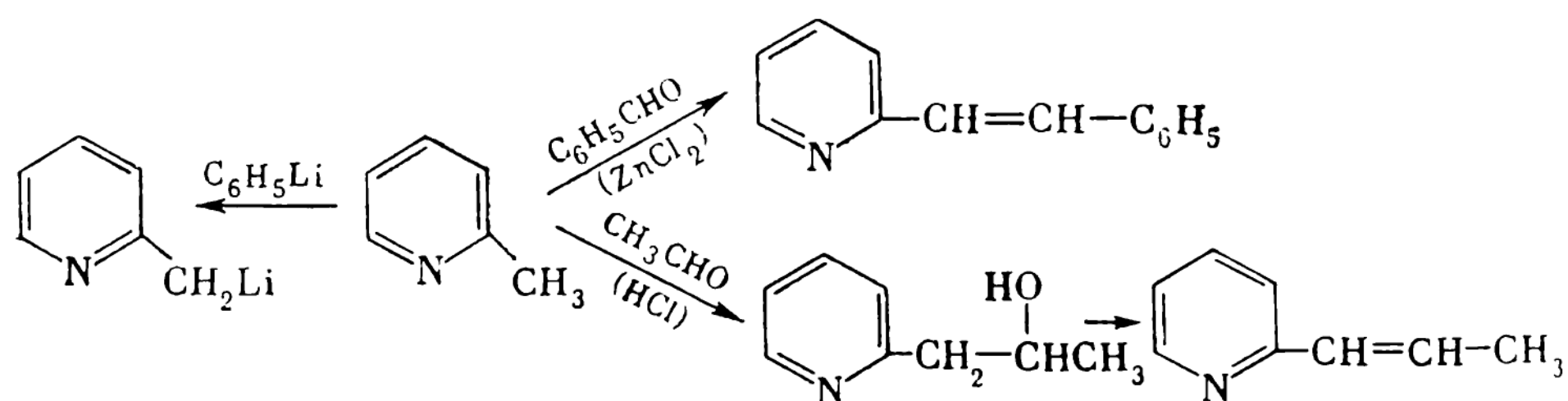
19. How is pyridine N-oxide prepared and why does it enter into electrophilic substitution reactions more readily than pyridine itself? What is the direction of electrophilic substitution reactions in this case?

20. In what positions do the mono- and dinitrations of the following compounds proceed: α -methoxypyridine, γ -hydroxypyridine, quinoline?

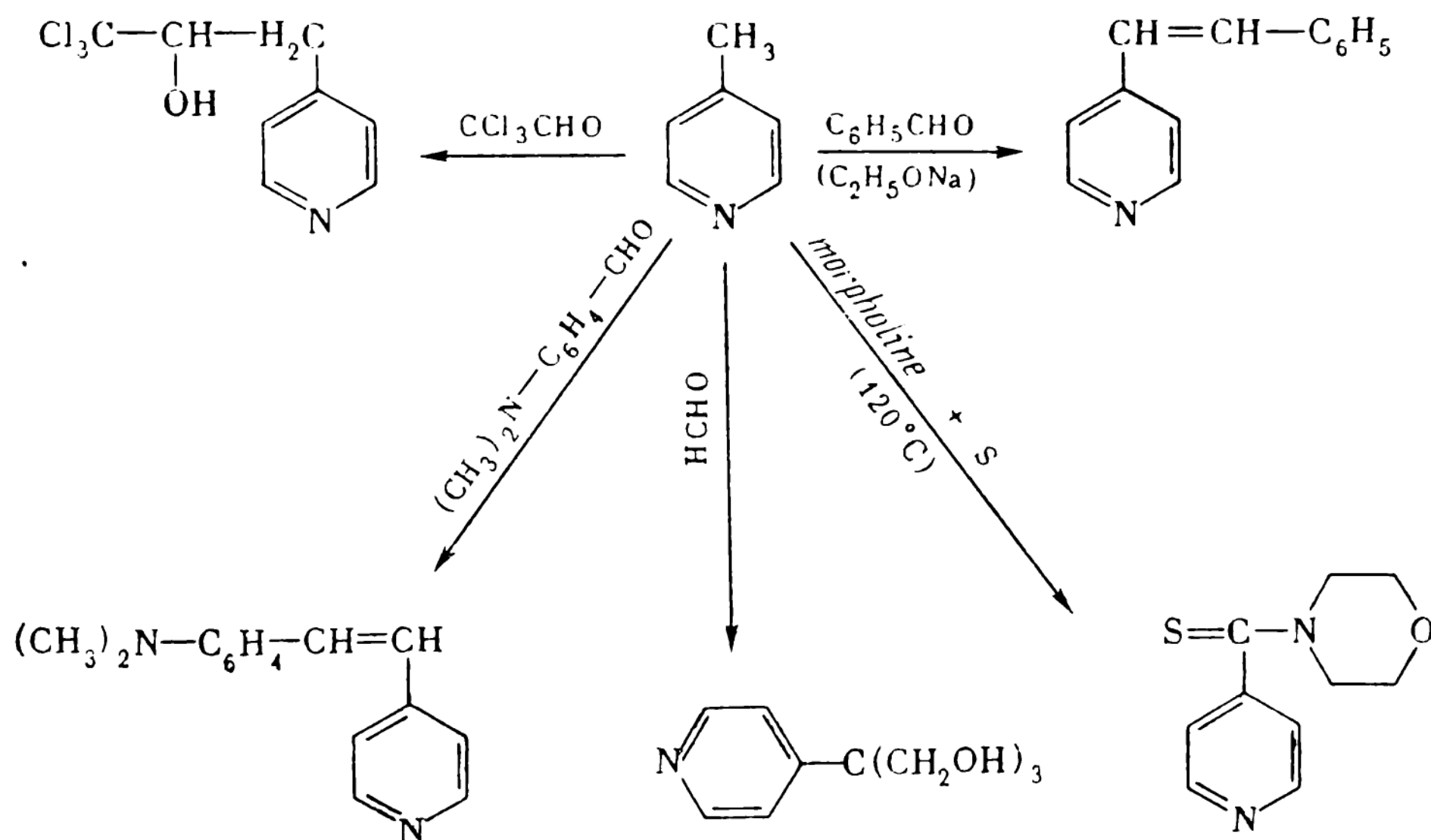
21. Compare the substitution reactions in pyridine and nitrobenzene by drawing up a table of the following type:

Type of reaction	Reaction conditions and the result	
	for pyridine	for nitrobenzene

22. What is the mechanism of the following reactions of α -methylpyridine:

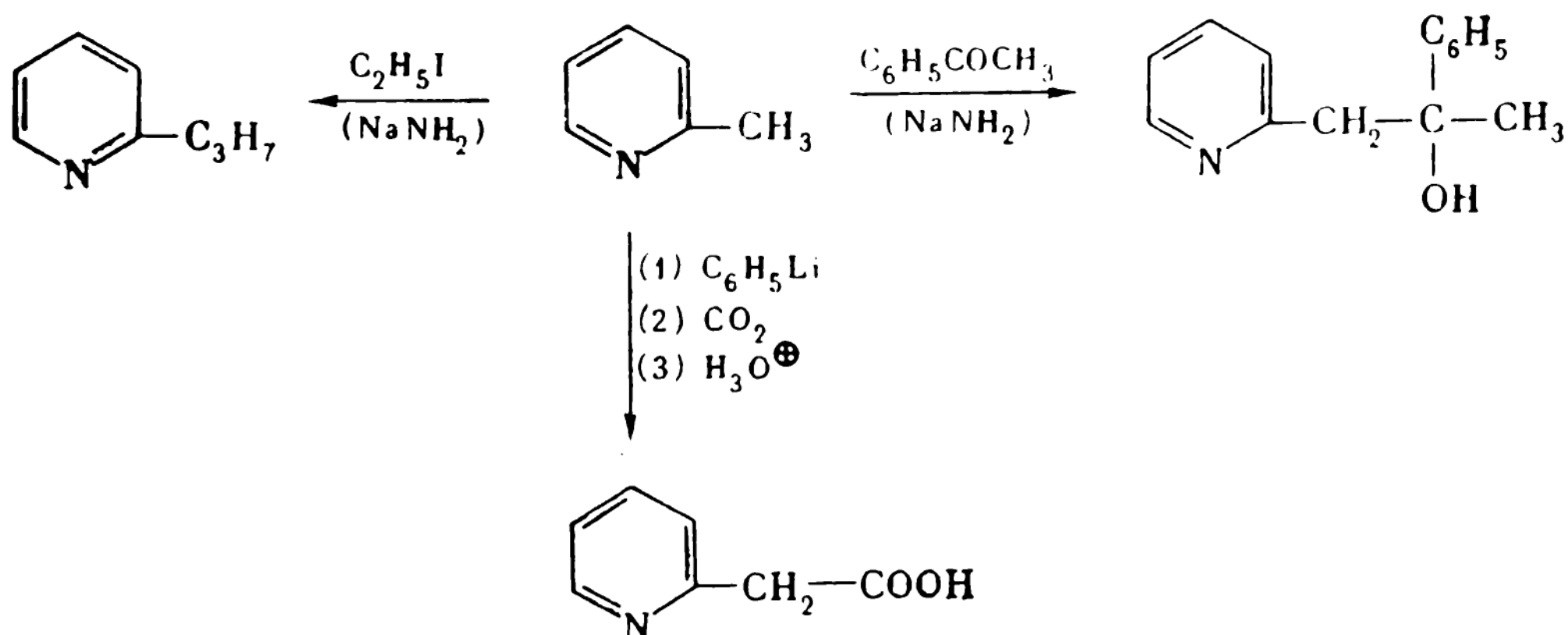


23. How can you account for the following conversions of 4-methylpyridine:

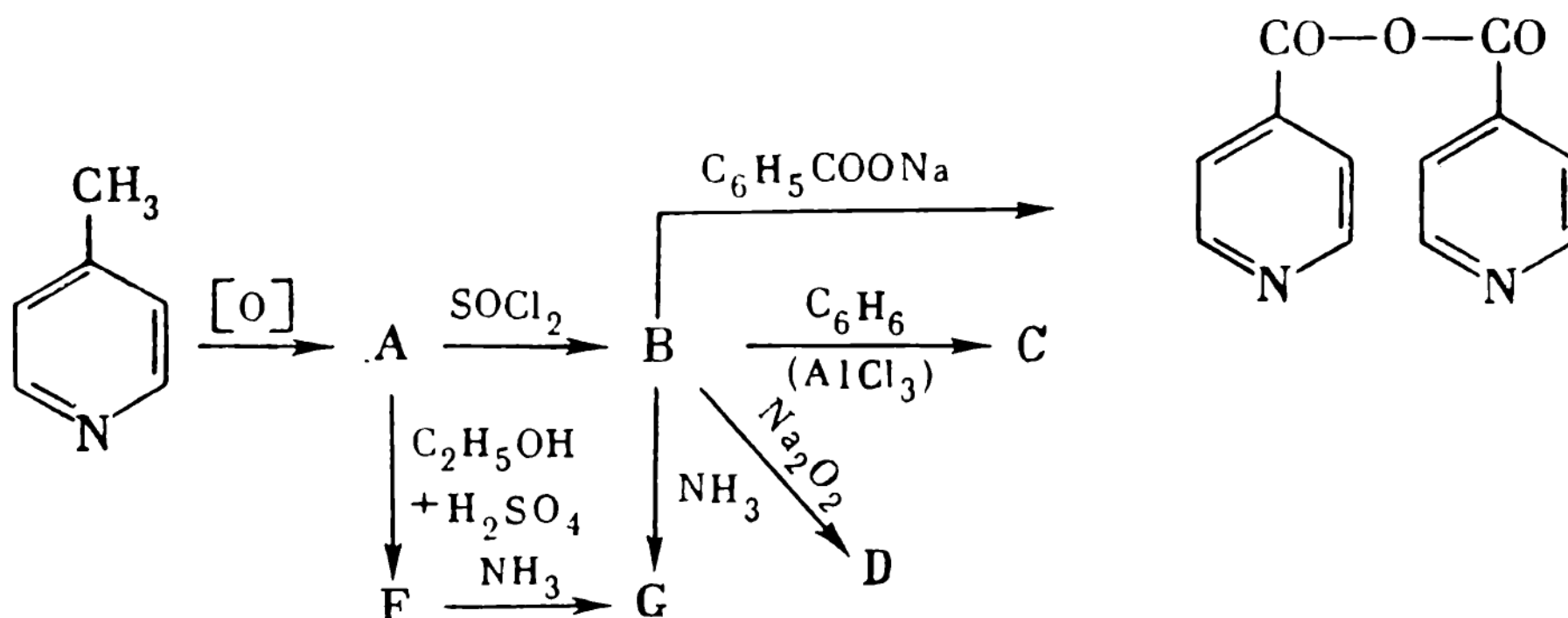


24. The action of formaldehyde on α -methylpyridine can lead to α -vinylpyridine. Explain this conversion.

25. What is the mechanism of the following conversions of α -methylpyridine:

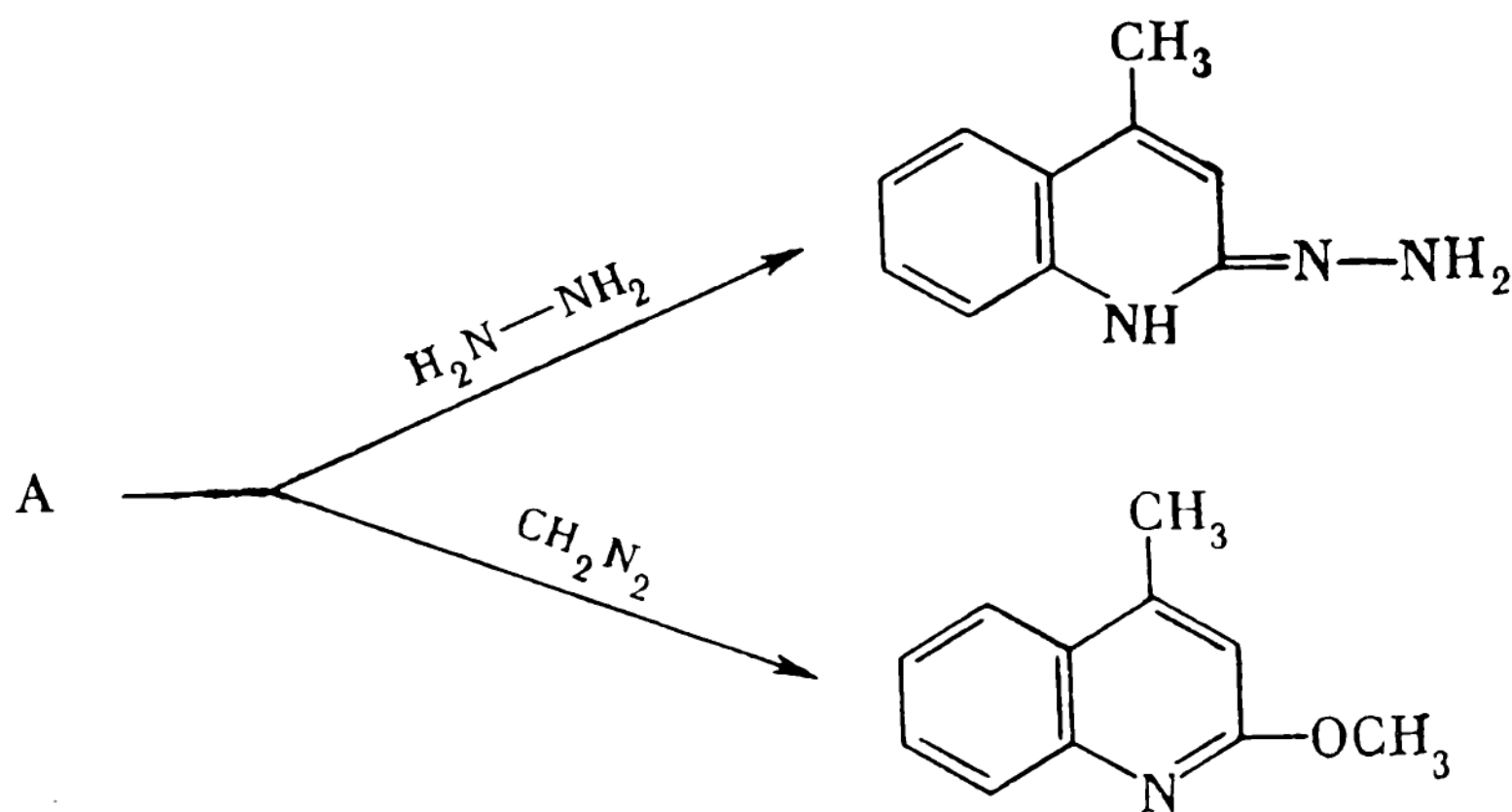


26. Identify the following scheme of conversions:

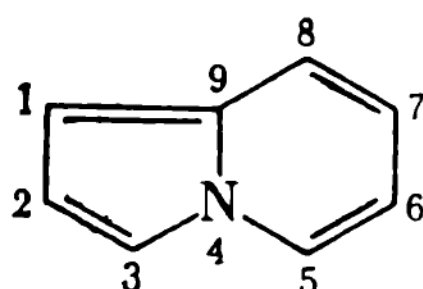


27. Write the scheme of the reactions of α -aminopyridine with: acetic anhydride, benzenesulphochloride, nitrous acid, and nitrosobenzene.

28. Name the starting material (A) and account for the formation of the following compounds:



29. To what position will there be directed the electrophilic and nucleophilic substitution in the so-called pyrrocoline having the formula



2. SYNTHESSES OF HETEROCYCLIC COMPOUNDS AND THEIR CONVERSIONS ¹

30. Synthesize 2,5-dimethylthiophene by using acetoacetic ester as the starting material.

31. Prepare 2,5-dimethylfuran from ethanol.

32. Prepare 2,3,4,5-tetramethylfuran from inorganic reagents and methyl alcohol.

33. Prepare tetramethylthiophene from methanol and ethanol.

34. Prepare 2,5-diphenylpyrrole from ethanol and toluene.

35. Prepare 2,5-dimethyl-3,4-diethylfuran from ethanol.

36. Prepare 2,5-diphenyl-3,4-diethylthiophene from toluene and ethanol.

37. Prepare 3,4-dimethylthiophene from ethanol.

38. Prepare 3,4-dimethylfuran from ethanol.

39. Prepare 3,4-diphenylthiophene from benzaldehyde and ethanol.

40. Suggest a scheme for synthesis of 2,5-diethylfuran from propyl alcohol.

41. Prepare α -ethylthiophene from ethanol.

42. Prepare 2-phenylthiophene from benzene and ethanol.

43. Prepare pyrrole from succinic acid without using other organic reagents.

44. Prepare furan from ethanol.

45. Prepare 2,4-dimethylpyrrole from ethanol.

46. Prepare tetrahydrofuran from acetylene and methanol.

47. Prepare α -thiophenecarboxylic acid from ethanol.

48. Prepare thienylcarbinol and thienoine from thiophene and methyl alcohol.

49. Prepare bis-(5-methylthienyl-2)-methane from thiophene and methyl alcohol.

50. Make 2- α -furyl-2-methylpentane from furan and *n*-propyl alcohol.

51. Make benzoylthenoylmethane from thiophene, benzene, and ethyl alcohol.

¹ In many problems of this section the solution is a chain of reactions which refer not only to the given topic but to the previous ones as well: these problems will be helpful in reiterating the entire material. Inorganic reagents are supposed to be available.

52. Suggest schemes for synthesis of the following compounds: (a) 2,3,5-trimethylindole; (b) 2-carboethoxyindole; (c) 5-nitro-2-methyl-3-ethylindole; (d) 5-bromo-2-carboxyindole; (e) 7-bromo-2-methylindolyl-3-acetic acid; (f) 1-keto-1,2,3,4-tetrahydrocarbazole.

Using benzene and the simplest compounds of the aliphatic series, how can you prepare the starting materials required for synthesis of the above compounds?

53. Prepare α -methylindole from benzene and propanol.

54. Prepare carbazole from benzene without resorting to other organic reagents.

55. Prepare carbazole from naphthalene without using other organic reagents.

56. Prepare 2-methyl-5-methoxyindole from benzene and the simplest alcohols.

57. Make 3-indolylacetic acid from benzene and the simplest alcohols.

58. Prepare 5-indolylcarboxylic acid from indole.

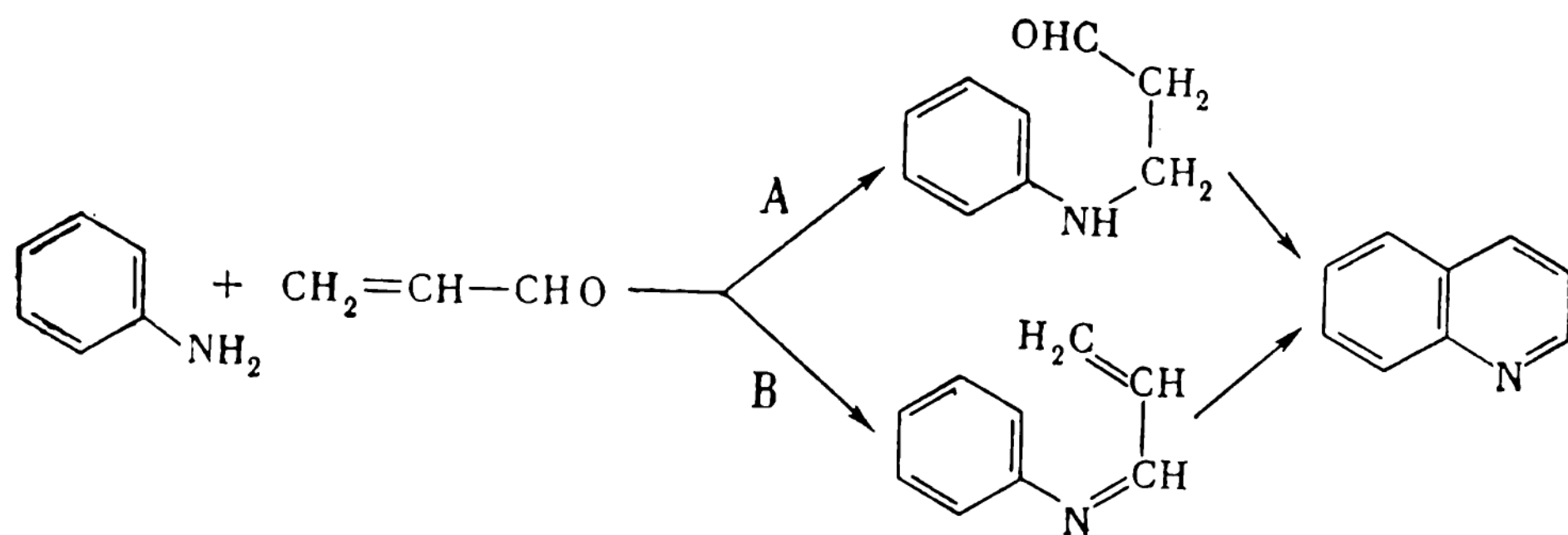
59. Naphthalene and acetic acid were used as the starting materials for synthesis of indigo. Suggest a possible scheme of this synthesis and discuss the mechanisms of the reactions involved.

60. Prepare 5,5-dibromoindigo.

61. Prepare 6,6-dibromoindigo from toluene.

62. Make 2,4,6-collidine (2,4,6-trimethylpyridine) from ethanol.

63. The course of the first step in the synthesis of quinoline from an aromatic amine and an unsaturated aldehyde may be written in two ways:



How could you prove by experiment which of these two versions is realized?

64. What compounds result when α - and β -naphthylamines are used in the Skraup synthesis?

65. What is the structure of alkylquinolines prepared by the Doebner-Miller reaction from: (a) propionaldehyde; (b) a mixture of acetaldehyde and acetone?

66. Suggest the schemes for the synthesis of: (a) 6-methoxy-4-methylquinoline; (b) 6-methoxy-5,7-dimethylquinoline; (c) 6-methoxyquinoline; (d) 7-chloro-2-methylquinoline; (e) 7-bromo-8-methylquinoline.

Show how, using the simplest organic compounds, you can prepare the starting materials required for these syntheses.

67. Prepare 2-ethyl-3-methyl-8-hydroxyquinoline from benzene and propyl alcohol.

68. Prepare 8-methyl-2-phenylquinoline from toluene and ethanol.

69. Prepare naphthine (β -naphthoquinoline or 5,6-benzoquinoline) from naphthalene and the simplest alcohols.

70. Prepare oxine (8-hydroxyquinoline) from benzene and the simplest alcohols.

71. Prepare isoniazid (the hydrazide of pyridine-4-carboxylic acid; it is a medicine) from pyridine.

72. Prepare vitamin PP (nicotinamide) from pyridine.

73. Prepare Coramine (diethylamide of nicotinic acid) from pyridine and other reagents.

74. Prepare α -picolinic acid from benzene and pyridine.

75. Prepare β -(α -pyridyl)-ethyl alcohol from α -picoline in two different ways.

76. Prepare quinaldic (α -quinolinecarboxylic) acid from benzene and ethanol.

77. Prepare N-ethylimide of 2,3-pyridinedicarboxylic acid from benzene and the simplest alcohols.

78. Prepare 5-iodo-8-hydroxyquinoline (a medicinal preparation called enteroseptole) from benzene and propanol.

79. Prepare the analytical reagent ferron (7-iodo-8-hydroxyquinoline-5-sulphoacid) from benzene.

80. Prepare dibromooxine (5,7-dibromo-8-hydroxyquinoline) from benzene and the simplest alcohols.

81. Prepare dichloroxine from benzene and the simplest alcohols.

82. Prepare phenazoxine (5-benzeneazo-8-hydroxyquinoline) from benzene and propylene.

83. Prepare sulphophenazoxine, i.e., 5-(4'-sulphobenzeneazo)-8-hydroxyquinoline from benzene and the simplest alcohols.

84. Prepare 2-methoxyquinoline from benzene and the simplest alcohols.

85. Prepare N-methylcarbostyrl from benzene and the simplest alcohols.

86. Prepare quinoline-5-carboxylic acid from naphthalene and glycerol.

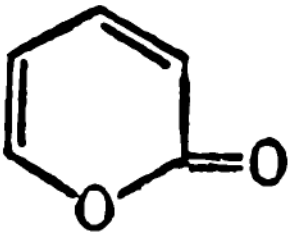
87. Prepare 5-hydroxy-8-ethylquinoline using 5-hydroxyquinoline.

88. Prepare 5-acetyl-8-hydroxyquinoline using benzene and the simplest alcohols.

89. Prepare α -phenylquinoline from benzene and *n*-propyl alcohol.

90. Prepare cumarin from phenol, acetic anhydride and inorganic reagents.

91. Prepare 4,6-dimethylcumarin from toluene and ethyl alcohol.

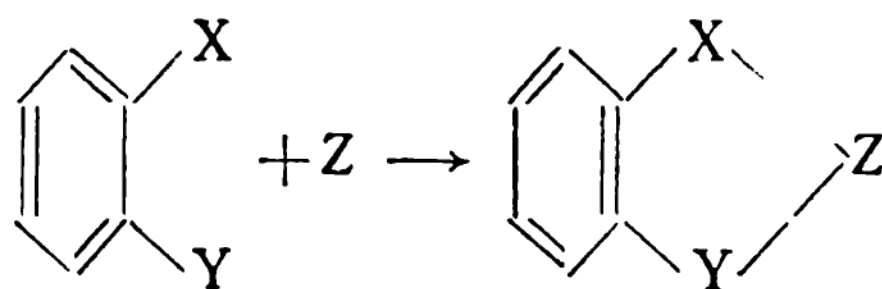
92. Prepare α -pyrone  from ethanol.

93. Prepare γ -pyrone from methanol and ethanol.

94. Prepare 2,6-dimethyl-4-methoxypyrylium iodide from ethanol.

95. What heterocyclic compounds can be prepared by the Beckmann rearrangement of indan-1-one oxime?

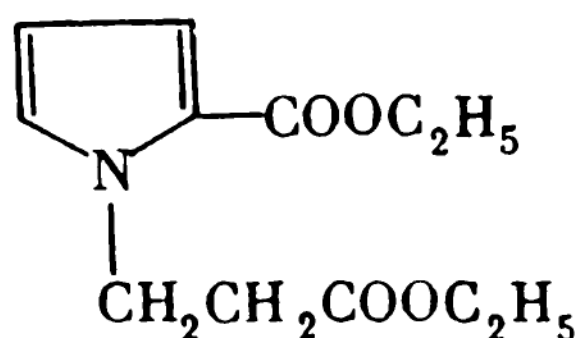
96. Using *ortho*-substituted compounds of the aromatic series, one can easily prepare various heterocyclic compounds:



Write the reactions you know in tabular form:

X	Y	Z	Structure and name of reaction product
---	---	---	--

97. What heterocyclic compounds are formed by the Dieckmann cyclization from: (a) ethyl N-cyanoethylaminoacetate; (b) di-(β -carbomethoxyethyl) sulphide; (c) di-(β -carboethoxyethylamine); (d) methyl ester of (carbomethoxyethyl) anthranilic acid; (e) dicarboethoxy derivative of the pyrrole series



98. Prepare 3-methyl-1-N-phenyl-5-pyrazolone from ethanol and benzene.

99. Prepare 1,3-diphenyl-5-pyrazolone from benzene and ethanol.

100. Prepare picrolonic acid (1-*p*-nitrophenyl-3-methyl-4-nitro-5-pyrazolone) from ethanol and benzene.

101. Prepare 1-phenyl-2,3-dimethyl-5-pyrazolone (a medicinal preparation called antipyrine) from the simplest alcohols and benzene.

102. Prepare the medicinal preparation amidopyrine (Pyramidon) which, according to its structure, is 1-phenyl-2,3-dimethyl-4-dimethyl-5-aminopyrazolone, from benzene and the simplest alcohols.

103. Prepare 4-N-methyl-N-(sodium methylenesulphonate)-amino-1-phenyl-2,3-dimethyl-5-pyrazolone (analgin) from the simplest alcohols and benzene.

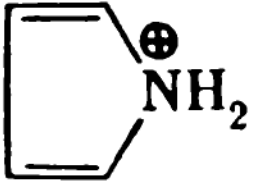
Answers

1. There may exist four disubstituted derivatives of furan with identical substituents (2,3-; 2,4-; 2,5-; 3,4-) and six disubstituted derivatives with different substituents (in the latter case the number of unsymmetrical 2,3- and 2,4-derivatives is doubled).

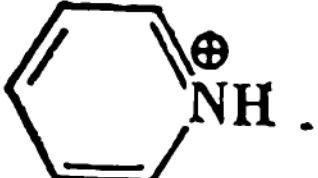
2. The aromatic system of pyrrole is built up with the participation of the free electron pair of the nitrogen atom (the aromatic sextet of electrons includes four π -electrons from two double C=C bonds and two p -electrons of the nitrogen atom). The aromatic system of pyridine is formed at the

expense of four π -electrons of double C=C bonds and two π -electrons of the double C=N bond, i.e., each of the atoms (five carbon atoms and one nitrogen atom) gives three electrons for the formation of three σ -bonds (two in the ring and one bond with hydrogen) and one electron for the formation of a system of common π -electron cloud. Hence, the bonds are formed by all the electrons of the carbon atoms and only three out of five electrons of the nitrogen, which has, as a result of this, a free electron pair, this pair being responsible for the basic nature of pyridine.

3. As indicated in answer 2, the electron pair of the nitrogen atom in pyrrole participates in the building-up of an aromatic system, whereas in pyridine it does not. Therefore the action of acidic agents capable of pulling out an electron pair of a nitrogen atom from the common π -electron aromatic system results in the breaking of the aromatic closed cyclic

structure and in the loss of aromaticity. The particle 

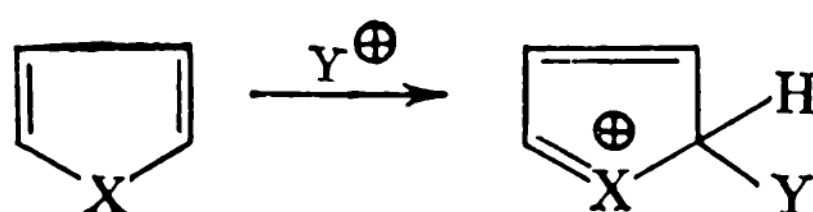
possesses the properties of an activated diene system and hence enters readily into further reactions leading to a complete loss of aromaticity (see, for example, J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965, Chapter 27). In the case of the pyridine system, acidic agents may attack the free electron pair of the nitrogen atom, leaving the aromatic

nucleus intact. The attack of the proton leads to .

4. The aromatic system of furan, like the nucleus of pyrrole, is built up with the participation of p -electrons of the oxygen atom, and therefore the action of acidic agents will also break the aromatic nucleus (see answer 3).

5. In the case of five-membered heterocycles the total π -electron density (six mobile electrons for five nuclei and, in the limiting case, for four C—H bonds) on the carbon atoms in the molecule (see J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965, Chapter 27) is found to be higher than in the benzene ring (six π -electrons for six nuclei and, in the

limit, for six C—H bonds). Besides, the attack on the aromatic system by electrophilic particles is facilitated by the tendency of nitrogen, oxygen and sulphur atoms to form “onium” structures as a result of the stabilization of a σ -complex



As a result of the operation of these factors, the electrophilic substitution reactions typical of aromatic systems in general proceed more easily. Such enhanced tendency to take part in electrophilic substitution reactions, which is especially pronounced in the case of furan and pyrrole, is sometimes called “superaromaticity”.

6. As known, in the benzene series, electron-donating substituents, particularly those having a large $+M$ -effect ($-\text{OR}$, $-\text{NR}_2$ groups) contribute to the activation of the aromatic nucleus. Therefore, with respect to reactivity in electrophilic substitution reactions, five-membered heterocycles are comparable with phenols, amines and even with phenolate anions (see the equation in answer 5). At the same time (see answers 2 and 3) the action of acidic agents may cause the electron pair of the heteroatom to be pulled out of the aromatic sextet, which leads to a decrease in the stability of such heterocycles and to their resinification.

7. The closest resemblance to benzene is exhibited by thiophene since the electronegativity of the sulphur atom and the tendency of sulphur to form sulphonium structures when acted on by acidic agents are less pronounced than in the case of nitrogen and oxygen atoms.

8. The activity in electrophilic substitution reactions increases in the sequence: benzene $<$ thiophene $<$ furan $<$ pyrrole.

9. In spite of the fact that the entire nucleus of the heterocyclic molecule is subject to activation, the strongest effect is exerted by the electron pair of the heteroatom when a substitution takes place into the α -position (in the neighbourhood of the heteroatom), which can be seen when considering the resonance structures of σ -complexes resulting from the electrophilic substitution reaction: upon substi-

tution into the α -position, the positive charge can be delocalized over three atoms, and upon substitution into the β -position over two atoms only.

10. The compounds listed may be arranged in the following sequence as regards the ease with which the reaction of electrophilic substitution takes place: benzene < toluene < mesitylene < thiophene < phenol < aniline < furan < pyrrole.

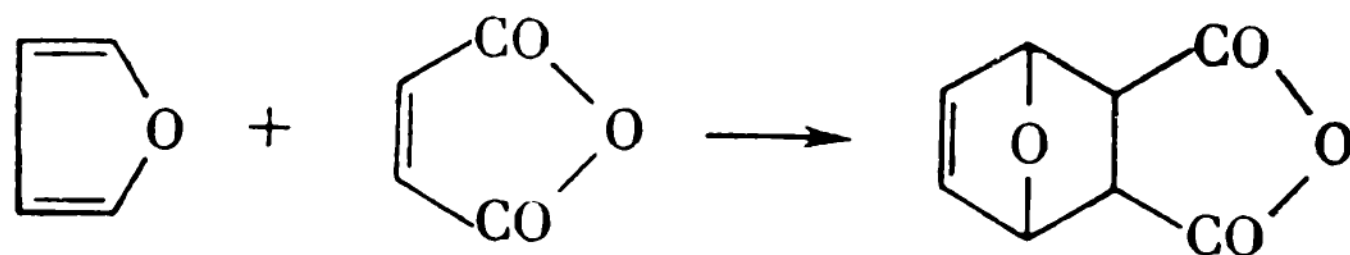
11. Most strongly inclined to substitution reactions are the 2- and 5-positions of the furan nucleus, and the electron-donating and electron-accepting substituents exert the same effect on the reactivity of the furan nucleus as in the benzene series.

Substitution reactions proceed: into the 5-position in the case of pyromucic acid and the ester of furan-2,4-dicarboxylic acid; and into the 4-position in the case of 5-methylpyromucic acid.

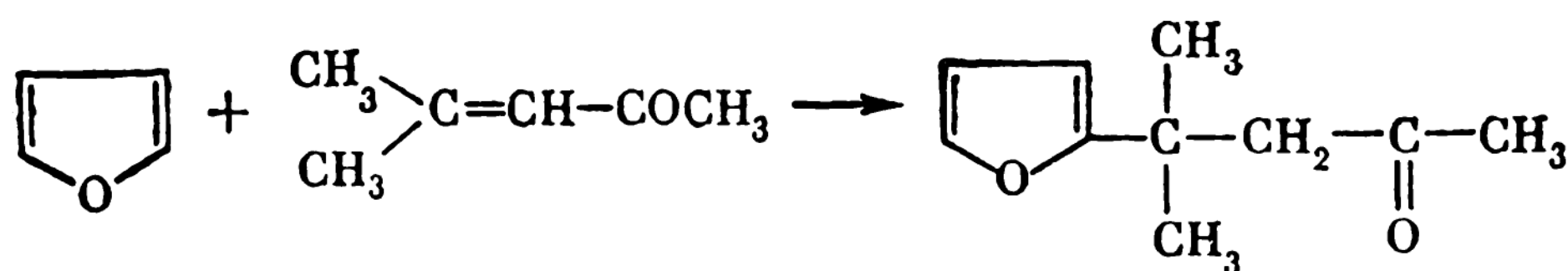
12. For separation of a mixture of benzene and thiophene with recovery of the starting materials use may be made of the mercuriation of thiophene with subsequent hydrolysis of chloromercurithiophene (under these conditions benzene remains intact).

In order to remove thiophene from benzene without regeneration of the former use may be made of the fact that thiophene is sulphonated (and also nitrated, chloromethylated, iodinated and acylated) much more readily than benzene.

13. Furan is an active dienophile and is capable of reacting with maleic anhydride to give the product of diene synthesis:



With mesityl oxide, furan reacts by the mechanism of the "substitutive addition" type:



14. Pyrrole reacts with two molecules of maleic anhydride by the substitutive addition mechanism (see 13).

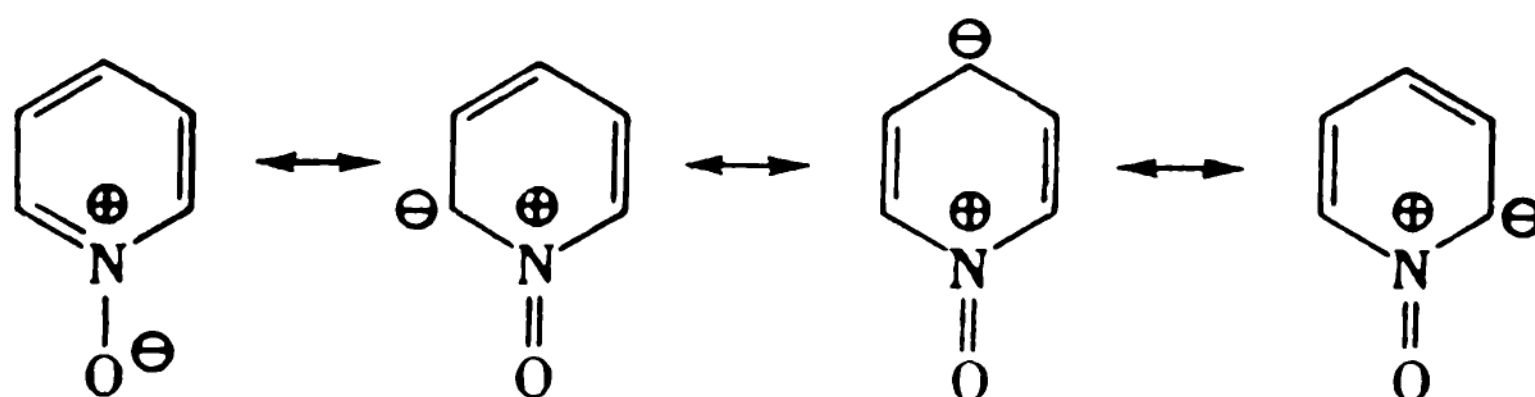
15. The Reimer-Tiemann reaction and the Kolbe-Schmitt reaction, i.e., the formylation aided by the action of chloroform and the carboxylation with carbon dioxide.

16. Use should be made of the ability of sylvan (α -methylfuran) to engage in diene synthesis (see answer 13). Under these conditions thiophene does not enter into diene synthesis and can be separated from the adduct, which, as distinct from thiophene, is soluble in alkali. In order to isolate sylvan one should take advantage of the reversibility of the diene synthesis, i.e., the adduct should be heated to a high temperature (subjected to pyrolysis).

17. The presence of a nitrogen atom possessing a greater electronegativity than a carbon atom (particularly in the sp^2 -valent state) results in an overall decrease in the electron density in the aromatic pyridine nucleus. The possibility of the attack by an electrophilic reagent (or a proton) across the free electron pair of the nitrogen and the formation of an ammonium structure also lower the ability of the pyridine nucleus to take part in electrophilic substitution reactions. For this reason pyridine should be compared with derivatives of the benzene series that contain electron-accepting substituents, for example, with nitro- and dinitrobenzenes.

18. The formation of α -aminopyridine by the action of sodium amide (amination according to Chichibabin); the formation of α -hydroxypyridine by fusing with sodium hydroxide; the formation of α -butylpyridine by heating with butyllithium.

19. Pyridine N-oxide is made by oxidizing pyridine with hydrogen peroxide. The following extreme cases of electron density distribution may be written for the resulting N-oxide:



It should be emphasized that such structures are not practically realizable and the distribution of electron density in the molecule is averaged (mesomeric).

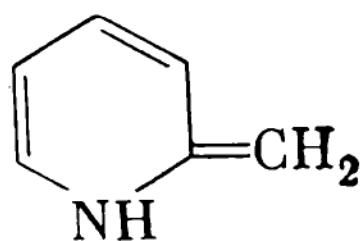
But still there is a certain partial negative charge in the α - and γ -positions. This contributes to the ease of the reaction of electrophilic substitution in the pyridine nucleus and to a corresponding orientation of the entering substituent.

20. The 2-methoxy group will activate the β -positions of the pyridine nucleus (an analogy with the *o*- and *p*-sites of the benzene ring, into which the substituent usually enters in electrophilic substitution reactions). The nitration will lead to 3- and 5-mononitro derivatives (coordinated orientation) and 3,5-dinitro derivative.

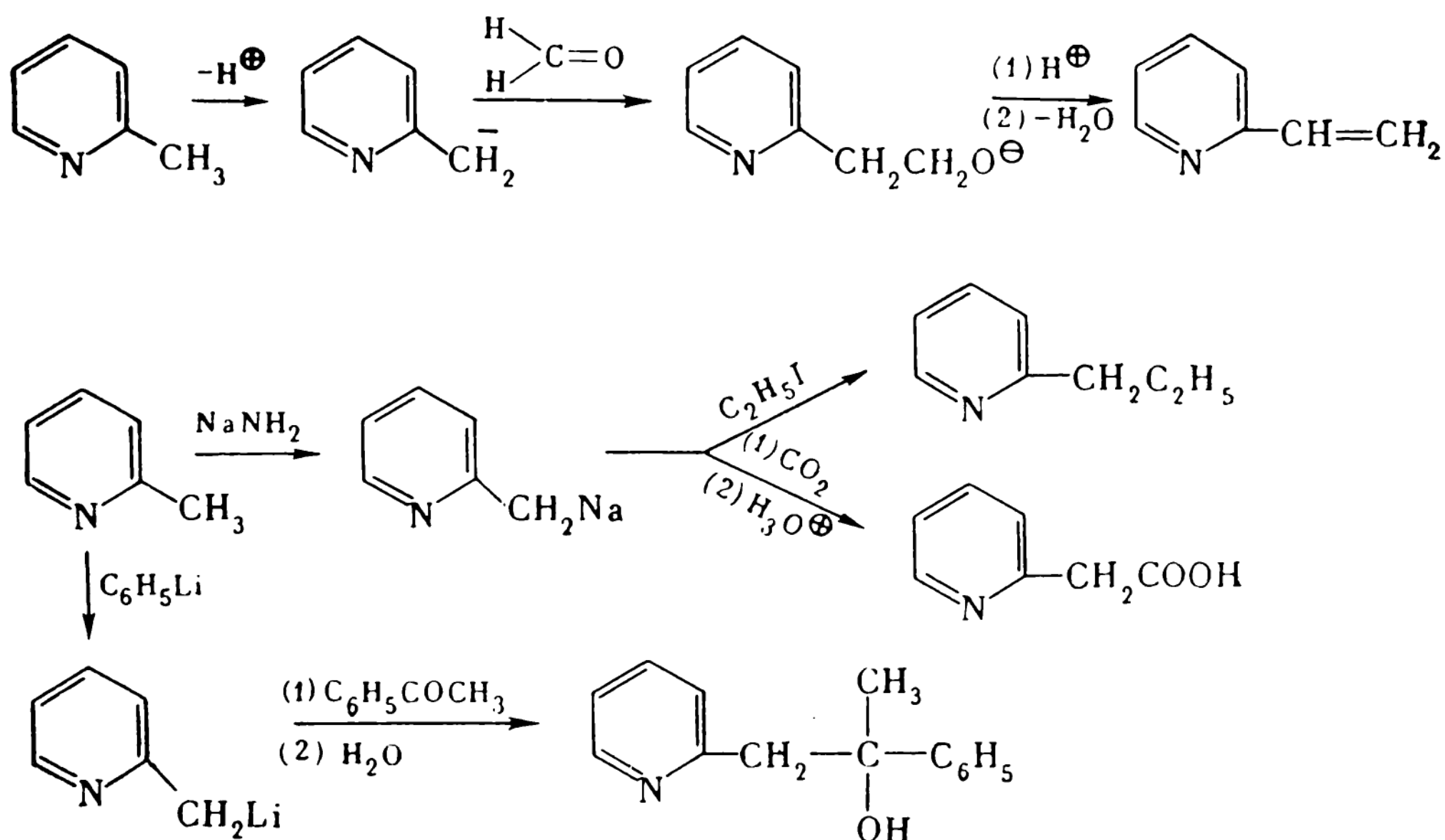
Analogously, γ -hydroxypyridine will give a mixture of 3-nitro- and 3,5-dinitro-4-hydroxypyridines. It is the benzene ring in the quinoline molecule that enters readily into electrophilic substitution reactions to form mononitro derivatives.

21. See A. N. Nesmeyanov and N. A. Nesmeyanov, *Fundamentals of Organic Chemistry*, v. 2 and J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965.

22-25. The methyl group in 2- and 4-methylpyridines (picolines) is activated under the influence of the electron-accepting pyridine nucleus. The reactions cited start either with the splitting off of the "acidic" hydrogen atom of the methyl group under the action of a base (the reaction with phenyllithium) or with the isomerization into the "methylene" structure

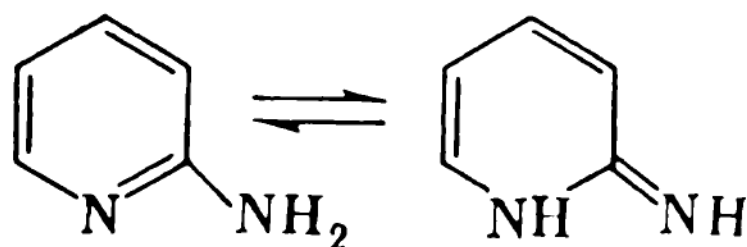


(see J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965, Chapter 27). There then take place reactions with carbonyl and other compounds according to a scheme analogous to the scheme of aldol-croton condensation:



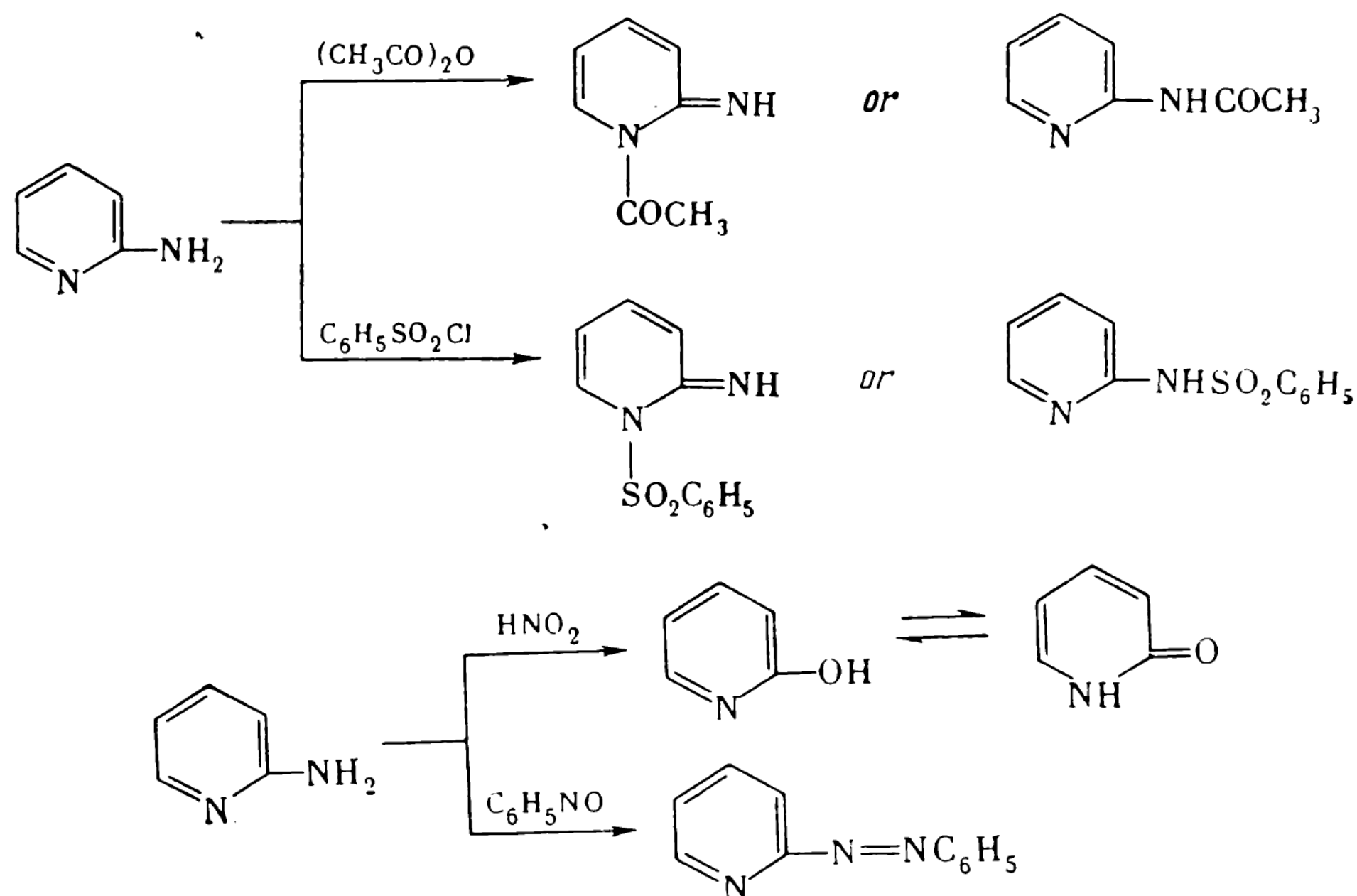
26. 4-Methylpyridine is oxidized to isonicotinic acid (A), which has the usual properties of carboxylic acids: it can be used to prepare ethyl ester (F), acid chloride (B) and from the latter there is prepared the anhydride. Compound B is introduced into the Friedel-Crafts reaction to give 4-benzoylpyridine (C); with sodium peroxide, there is obtained the peroxide of isonicotinic acid (D), and with ammonia, an amide (G).

27. 2- and 4-Aminopyridines show a dual reactivity and they react as if they exist in two forms: the amine and the imine form (see J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, 1965, Chapter 27).



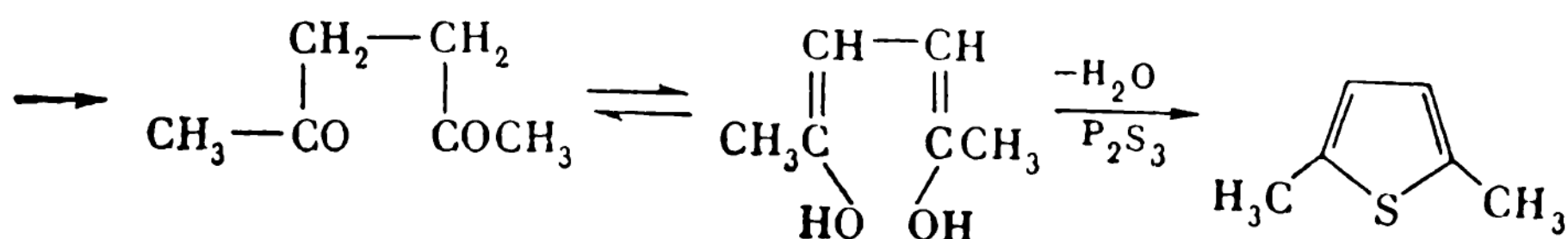
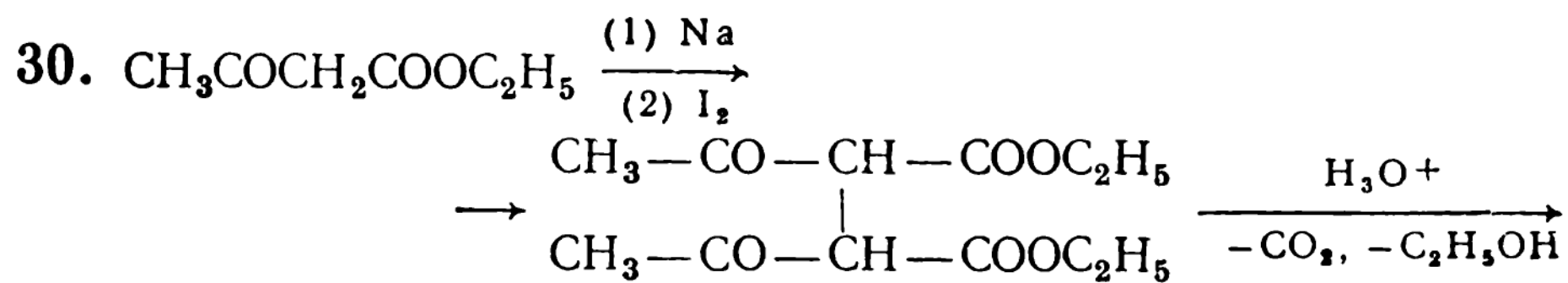
The reactions with the reagents indicated may yield derivatives both for the nitrogen atom of the amino group and the

one in the cycle.



28. The starting material is 2-hydroxy-4-methylquinoline, which exists in two tautomeric forms—hydroxyquinoline and quinolone.

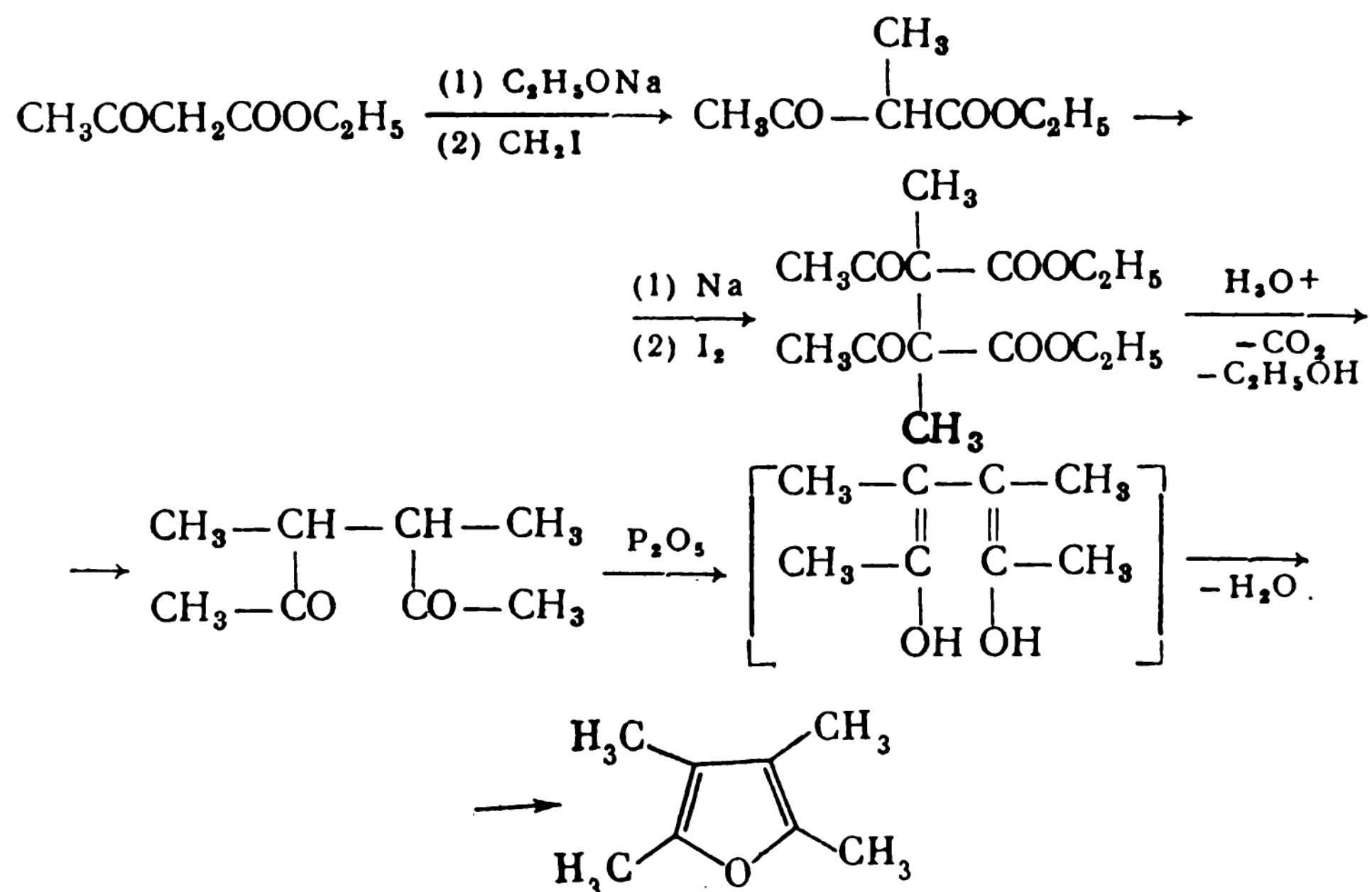
29. Pyrrocoline is a combination of a pyrrole (more active) and a pyridine (less active) nuclei. Substitution reactions may be arranged in order of decreasing ease of their occurrence for various sites in pyrrocoline in the following sequence: $3 > 2 > 1$ (α - and two β -positions of pyrrole, the β -1-position being deactivated by the pyridine nucleus more strongly than the position 2) $> 7 > 8 > 5$ (β -, α -, and γ -positions of the pyridine nucleus).



31. The synthesis is analogous to the one given above (see 30): acetoacetic ester is first prepared; no recourse must be made to the action of phosphorus trisulphide or pentasulphide.

32. From calcium carbide there is first obtained acetylene, then ethyl alcohol and acetic acid and, finally, ethylacetate and acetoacetic ester.

Then use is made of the synthesis of 1,4-diketones from esters of β -ketoacids



33. The synthesis is analogous to the one given above (see 32), with the only exception that at the last stage 1,4-diketone should be acted on by phosphorus trisulphide or pentasulphide. One may also convert tetramethylfuran to tetramethylthiophene according to the Yuriev reaction.

34. For synthesis, it is most convenient to make use of the preparation of five-membered heterocycles via 1,4-dicarbonyl derivatives, and in this case benzoylacetic ester should be used. The last-named compound is made from acetoacetic ester (the starting material is ethanol) and benzoyl chloride (the starting material is toluene). Benzoylacetic ester is converted to a sodium derivative, which is coupled by the action of iodine and decarboxylated to give 1,4-diphenylbu-

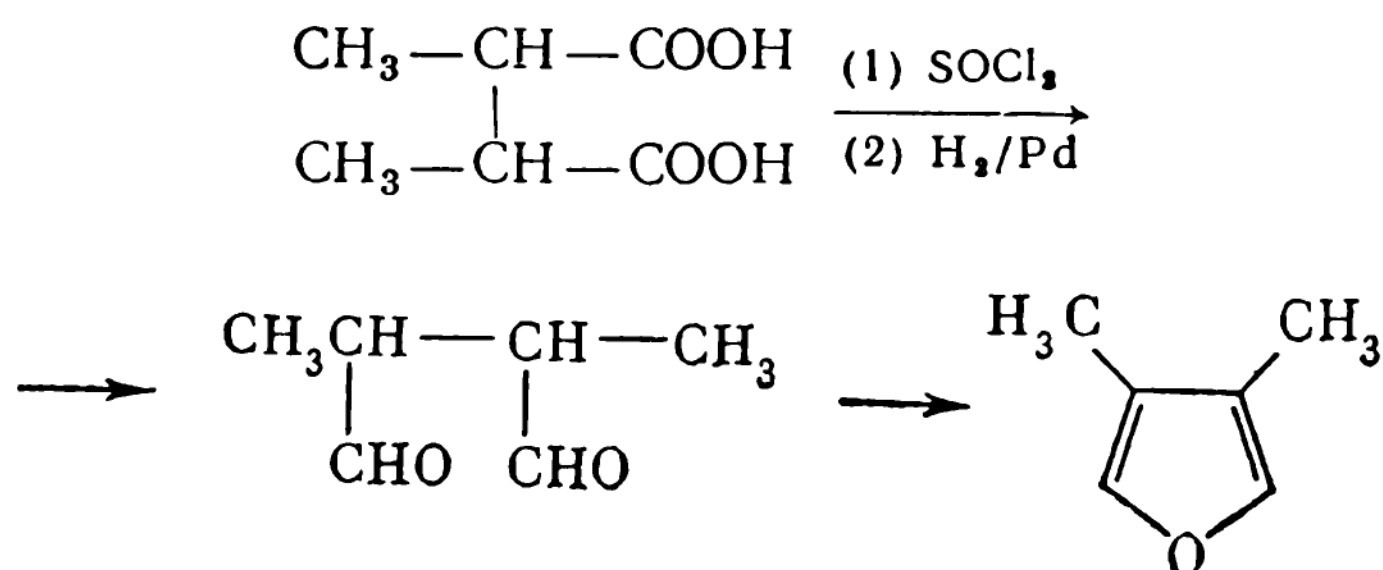
tane-1,4-dione. The last-named compound is converted by the action of ammonia to 2,5-diphenylpyrrole.

35. The synthesis is analogous to the one given in Problem 32, but for acetoacetic ester to be alkylated, use should be made of ethyl iodide.

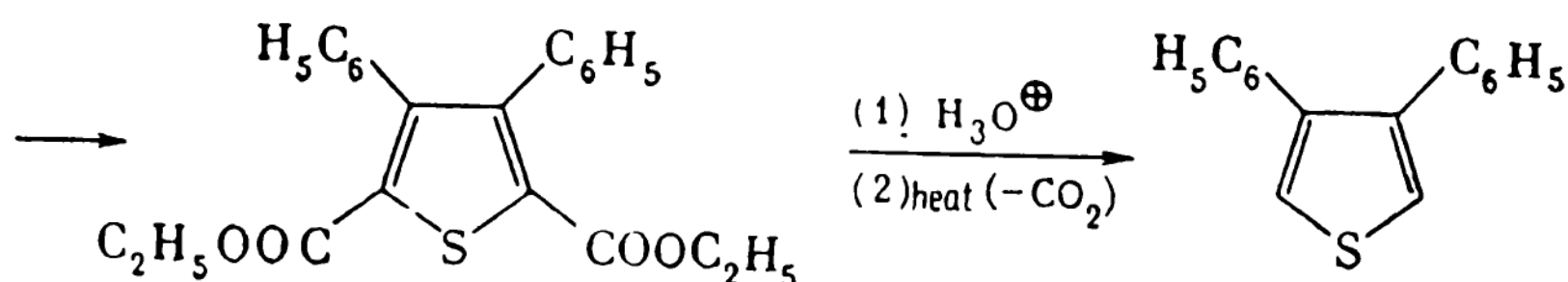
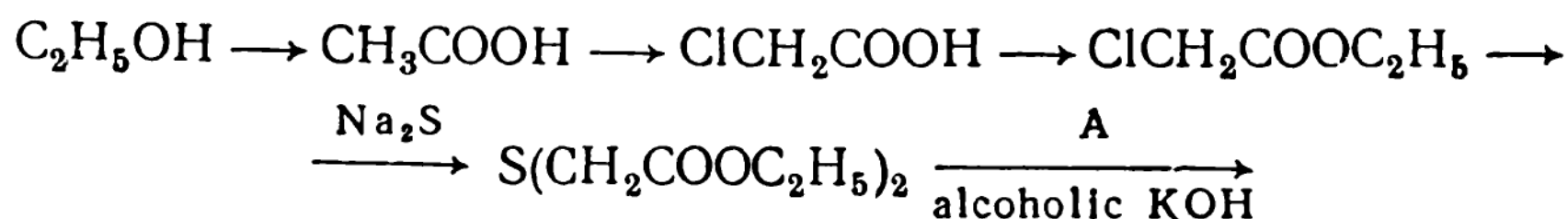
36. The synthesis is analogous to the syntheses given in Problems 34 and 35. It is the sodium derivative of benzoylacetic ester that should be subjected to alkylation with ethyl iodide.

37. Bis-methylacetoacetic ester is subjected to acid splitting and the resulting 2,3-dimethylsuccinic acid is heated with phosphorus trisulphide.

38. The synthesis is analogous to the one given above (see 37), but the resulting acid is preliminarily reduced to a dialdehyde according to Rosenmund:



39. Direct incorporation of a phenyl radical into the 3,4-positions in the synthesis of 3,4-dicarbonyl compounds is impossible, and use should therefore be made of an indirect way:



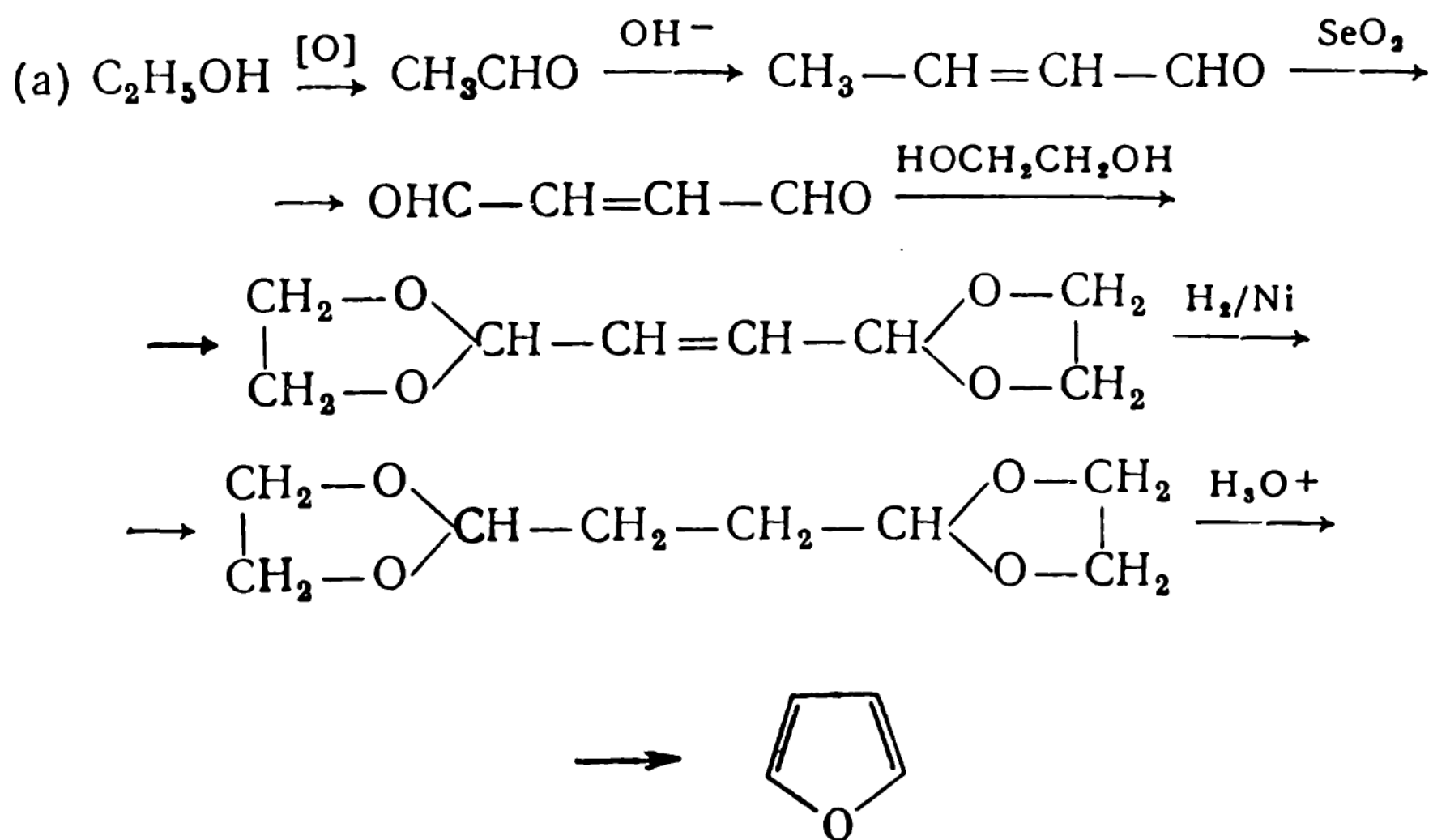
40. Dipropyl ether and *n*-propyl bromide should first be synthesized from *n*-propyl alcohol and then propylmagnesium bromide is made in dipropyl ether and acetylene passed into a solution of an organomagnesium compound (acetylene is prepared from calcium carbide; one mole of acetylene is taken for 2 moles of RMgX). To the resulting Iotsich complex (dibromodimagnesium acetylene) there are added 2 moles of propionaldehyde synthesized by oxidation of propyl alcohol. The resulting oct-4-yne-3,6-diol must be converted by catalytic hydrogenation to octane-3,6-diol and the latter oxidized to the corresponding diketone. By the action of phosphorus pentoxide (see answer 30) this diketone gives 2,5-diethylfuran.

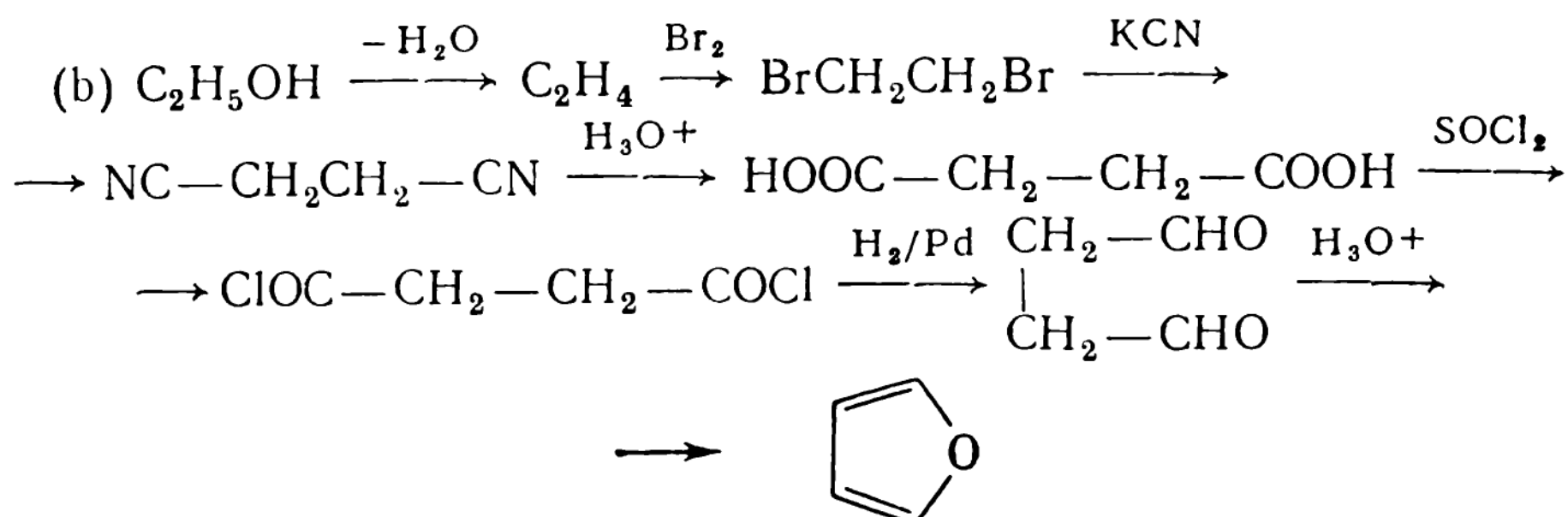
41. Acetoacetic ester is alkylated first with ethyl bromide and then with ethyl chloroacetate. Then acid splitting is effected and α -ethylsuccinic acid is made and treated with phosphorus trisulphide.

42. From ethanol there is obtained succinic acid, whose anhydride is introduced into the Friedel-Crafts reaction. The resulting γ -keto acid is converted by the action of phosphorus trisulphide into α -phenylthiophene.

43. Succinic acid is converted to succinimide, which is reduced with zinc dust to pyrrole.

44. Furan can be made either via crotonaldehyde or via succinic acid by the following schemes:





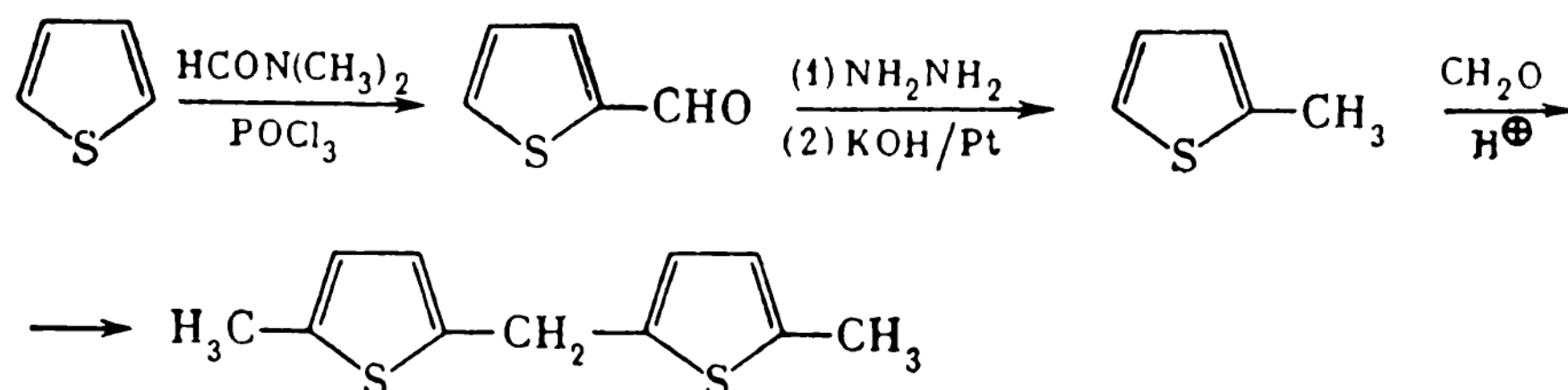
45. Sodiaoacetoacetic ester is condensed with α -bromopropionic ester; the resulting product after saponification and decarboxylation gives 4-keto-2-methylpentanoic acid, whose chloride is reduced according to Rosenmund to 4-keto-2-methylpentanal, which is converted on heating in an acidic medium into 2,4-dimethylfuran and then, by the Yuriev reaction, to 2,4-dimethylpyrrole.

46. Butyne-1,4-diol is made from acetylene and formaldehyde, and reduced with hydrogen over nickel to butane-1,4-diol; the latter when acted on by sulphuric acid gives tetrahydrofuran.

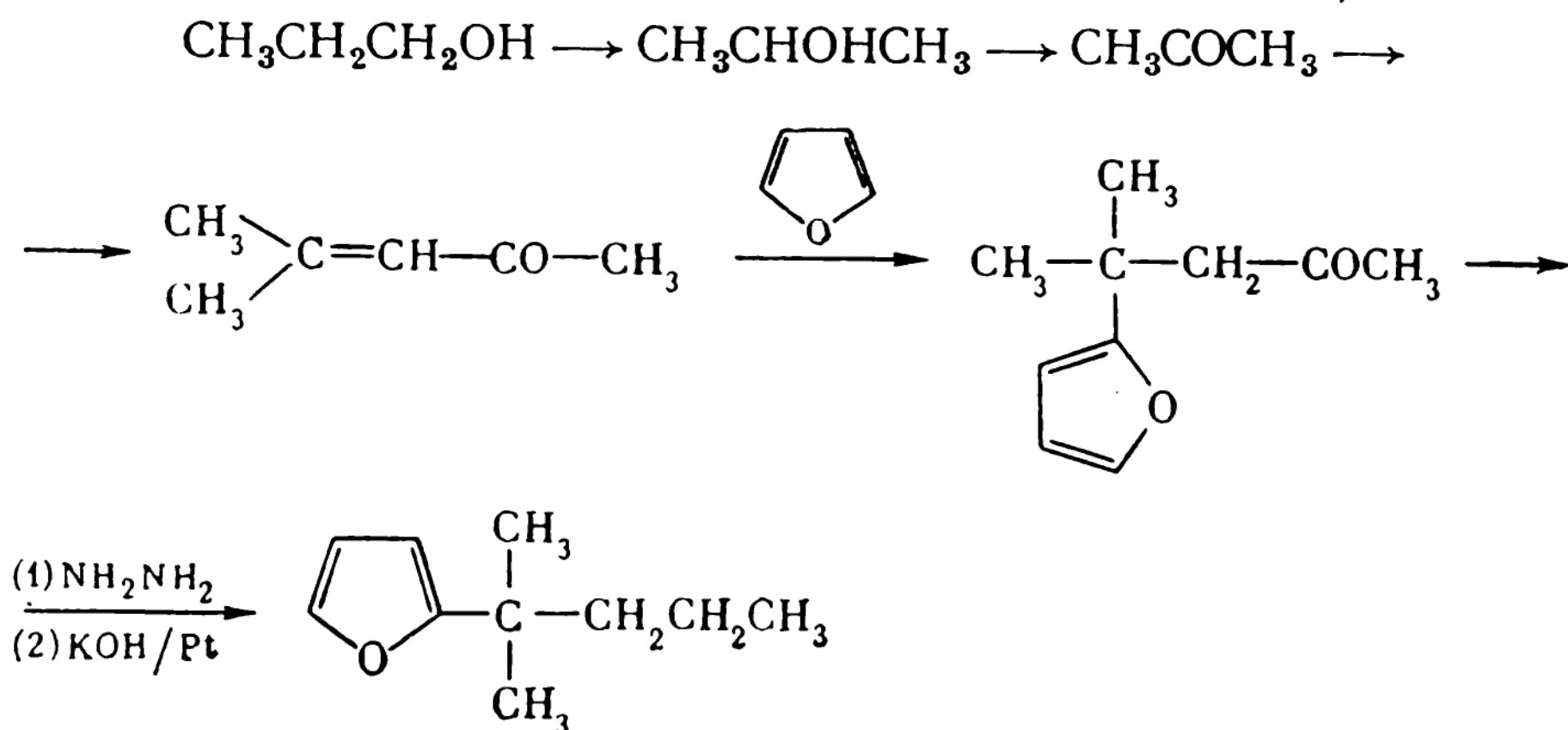
47. One should take advantage of the stability of the thiophene nucleus against oxidation and carry out the oxidation of 2-methylthiophene made via 4-ketopentanoic acid (which is prepared in the same way as in 41).

48. Methanol is oxidized to formic acid, from which dimethylformamide is made and used to formylate thiophene according to Vilsmeier. Under the conditions of the Cannizzaro reaction the resulting α -thiophenic aldehyde gives thienoine and when it is reduced with lithium aluminium hydride, α -thienylcarbinol is formed.

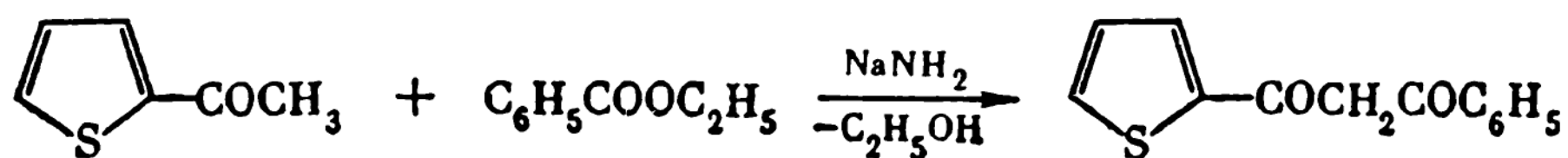
49. As indicated in example 48, α -thiophenic aldehyde should first be prepared, which must then be reduced according to Kishner to α -methylthiophene, which is condensed with formaldehyde (the condensation takes place in the α -position):



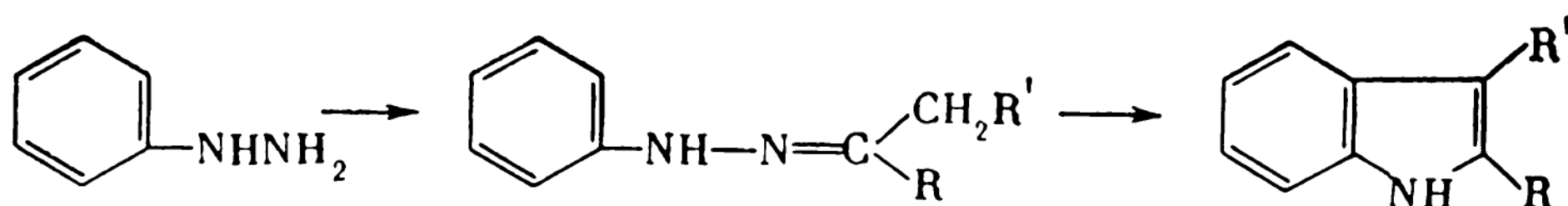
50. Use should be made of the reaction of substitutive addition of furan to mesityl oxide (see Problem 13):



51. Thiophene is acylated with acetyl chloride to give methyl thienyl ketone. From benzene there is first obtained bromobenzene, then benzoic acid and its ester. Then an ester condensation is carried out:



52. Use the Fischer synthesis of indoles¹:

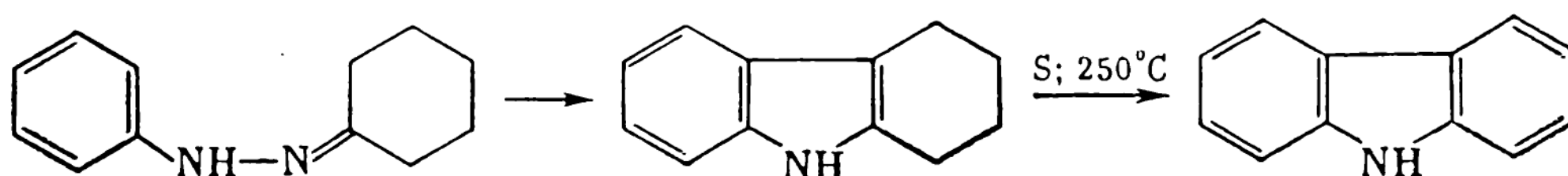


The starting materials are: (a) *p*-tolylhydrazine and methyl ethyl ketone; (b) phenylhydrazine and ethyl ester of pyrrocemic acid; (c) *p*-nitrophenylhydrazine and methyl-*n*-propyl ketone; (d) *p*-bromophenylhydrazine and ethyl pyrrocemate (the resulting compound must be saponified); (e) *o*-bromophenylhydrazine and ethyl ester of levulinic acid (the latter can be made from acetoacetic ester and ethyl chloroacetate); (f) phenylhydrazine and cyclohexane-1,2-dione (which is prepared from cyclohexanone by oxidation of selenium dioxide; diketone monophenylhydrazone is introduced into the reaction).

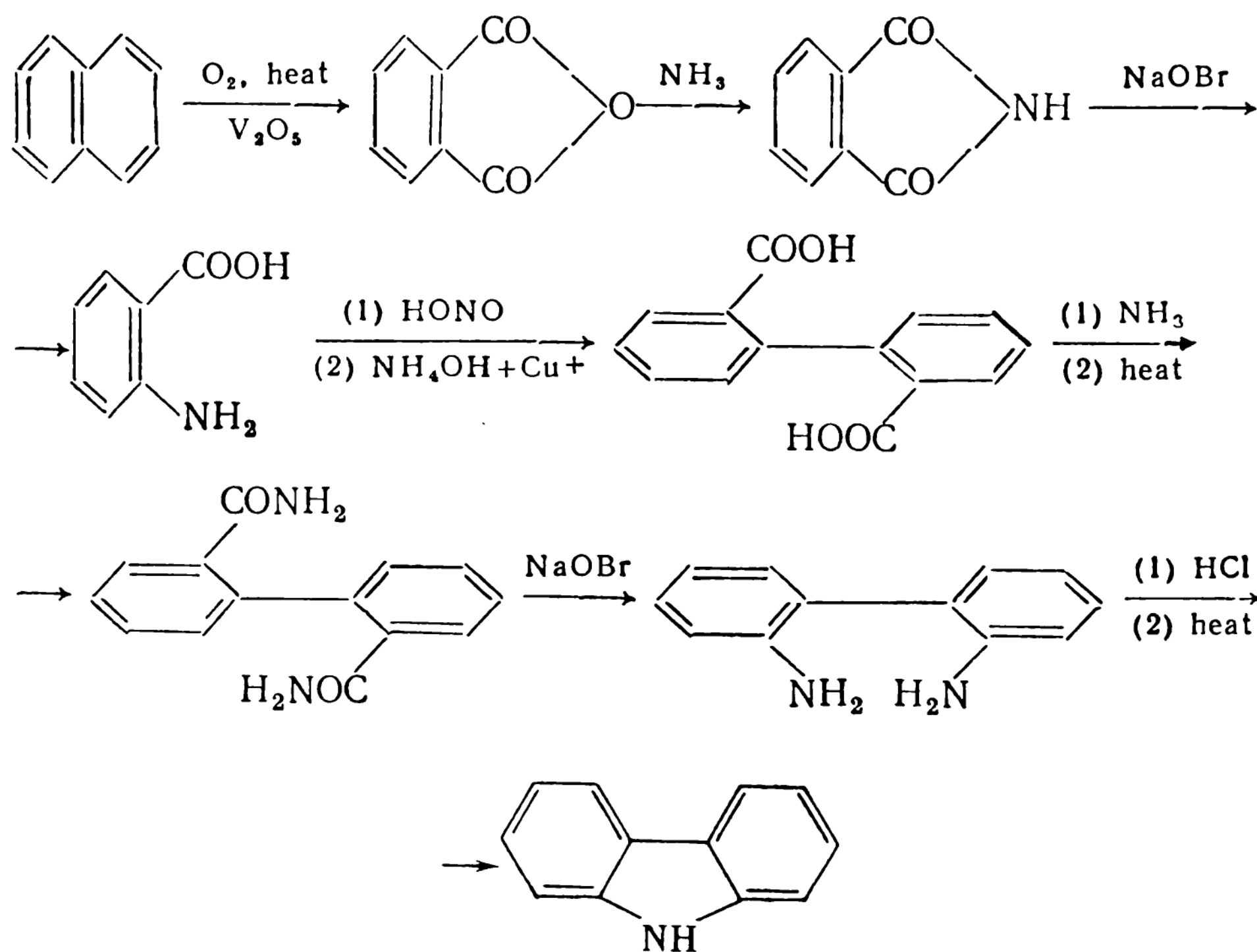
¹ For synthesis of starting arylhydrazines see Chapter 8.

53. Use should be made of the Fischer reaction between propionaldehyde and phenylhydrazine.

54. From benzene there is obtained aniline, which is used to prepare phenylhydrazine and (via phenol) cyclohexanone. These starting materials are used in the Fischer reaction to prepare tetrahydrocarbazole, which is then dehydrated:



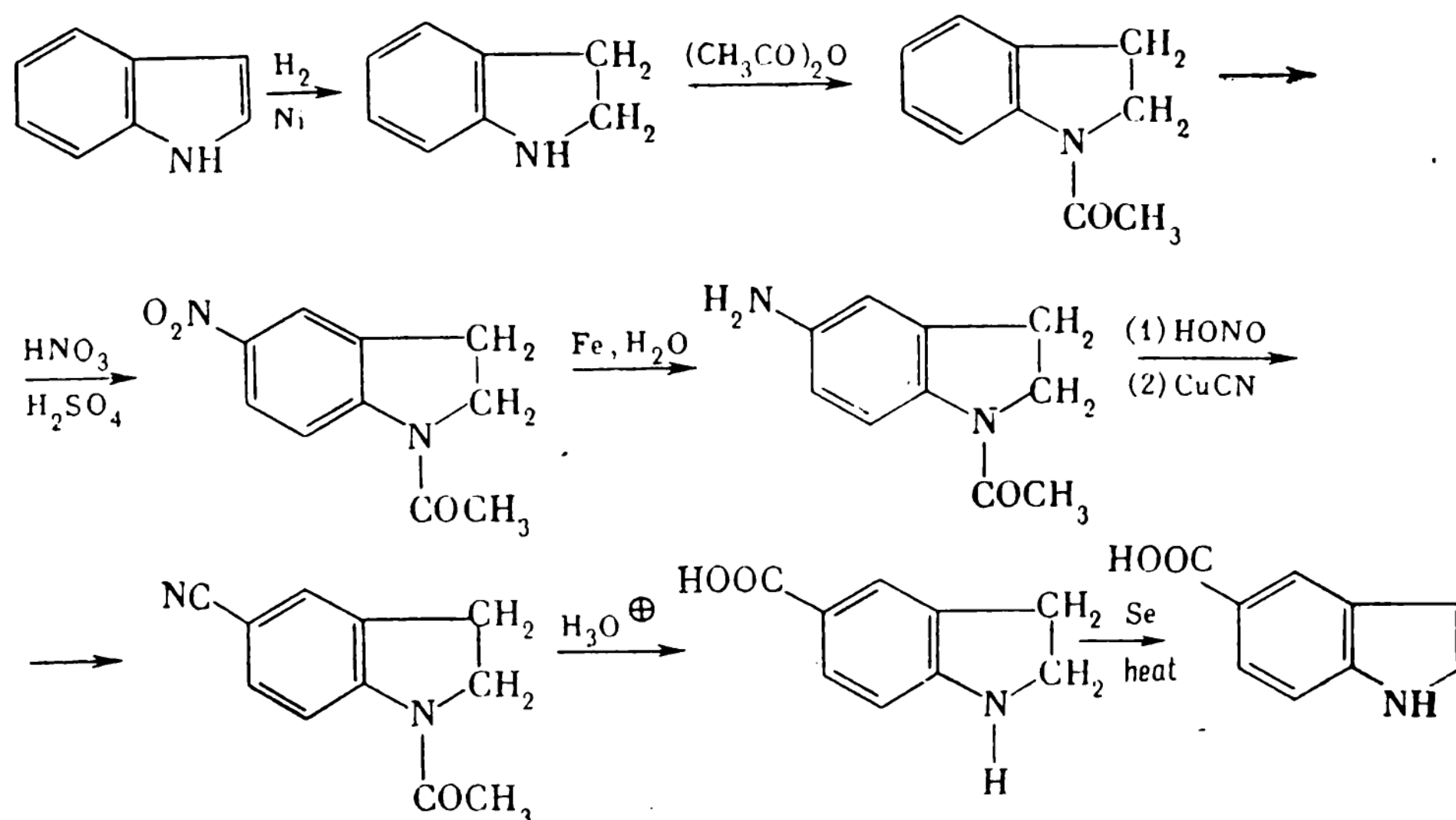
55. Anthranilic acid is first made, then diphenic acid and 2,2'-diaminodiphenyl:



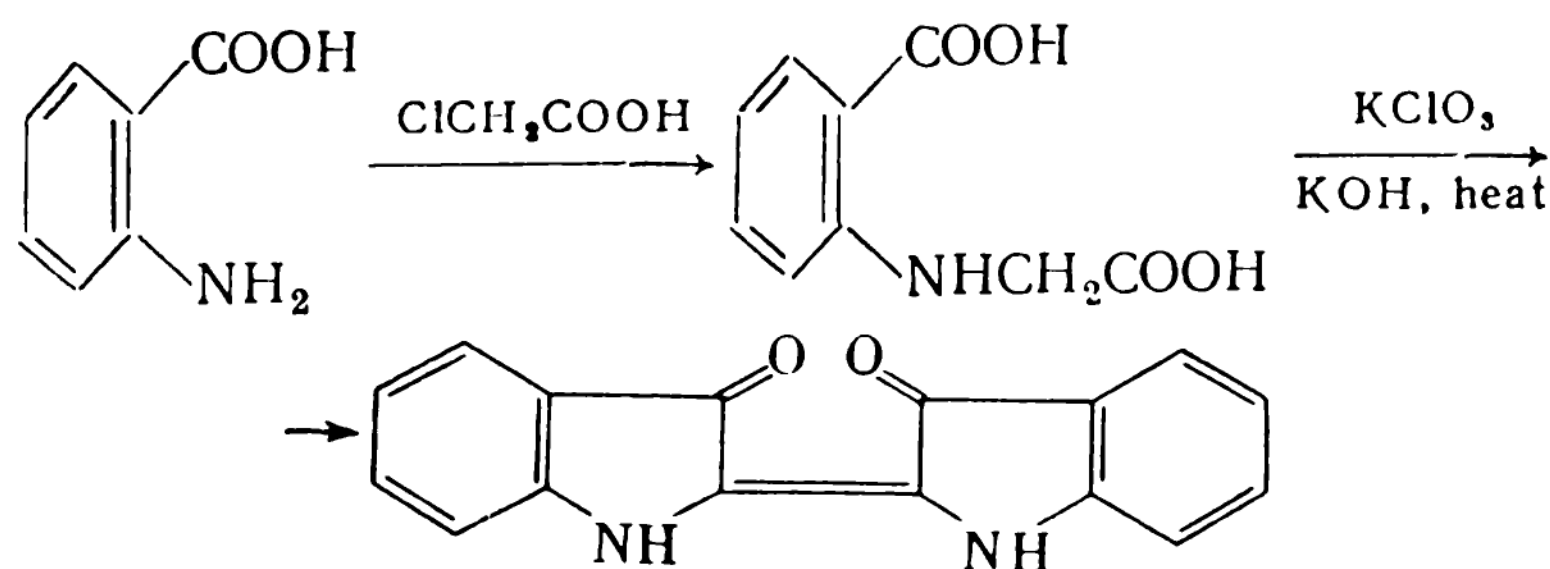
56. *p*-Methoxyphenylhydrazine and acetone are prepared and then use is made of the Fischer method.

57. Use must be made of the Fischer method; but first β -cyanopropionic aldehyde and phenylhydrazine are to be made.

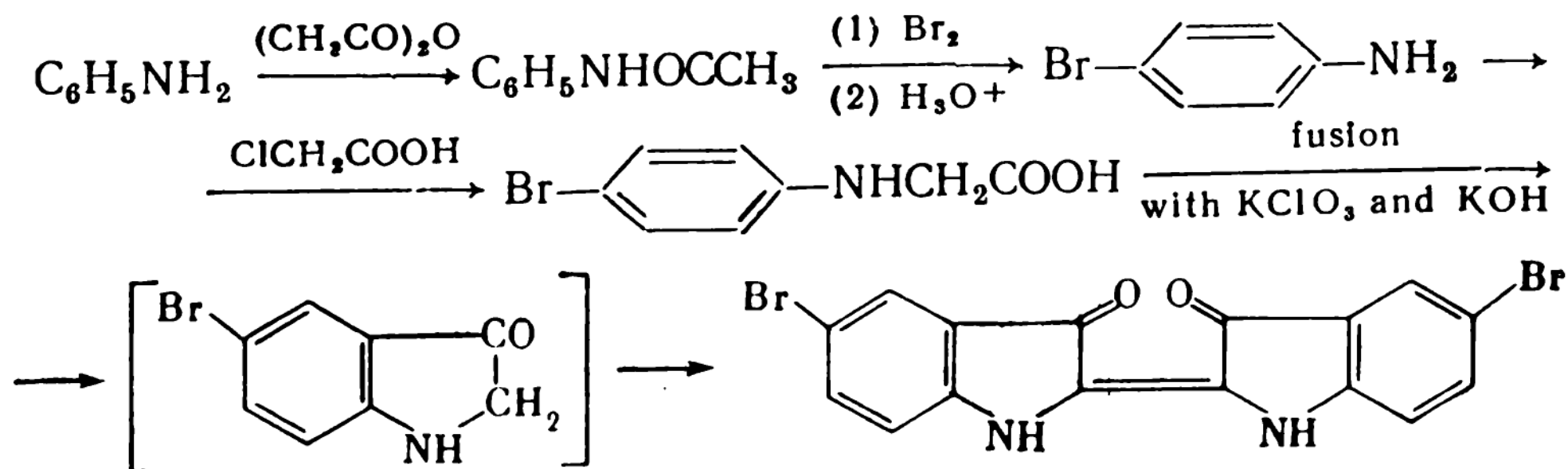
58. To solve the problem, a series of conversions in the indole nucleus must be carried out:



59. What is meant here is the classical Heimann synthesis: anthranilic acid is made from naphthalene (see answer 55) and then the following reactions are carried out:

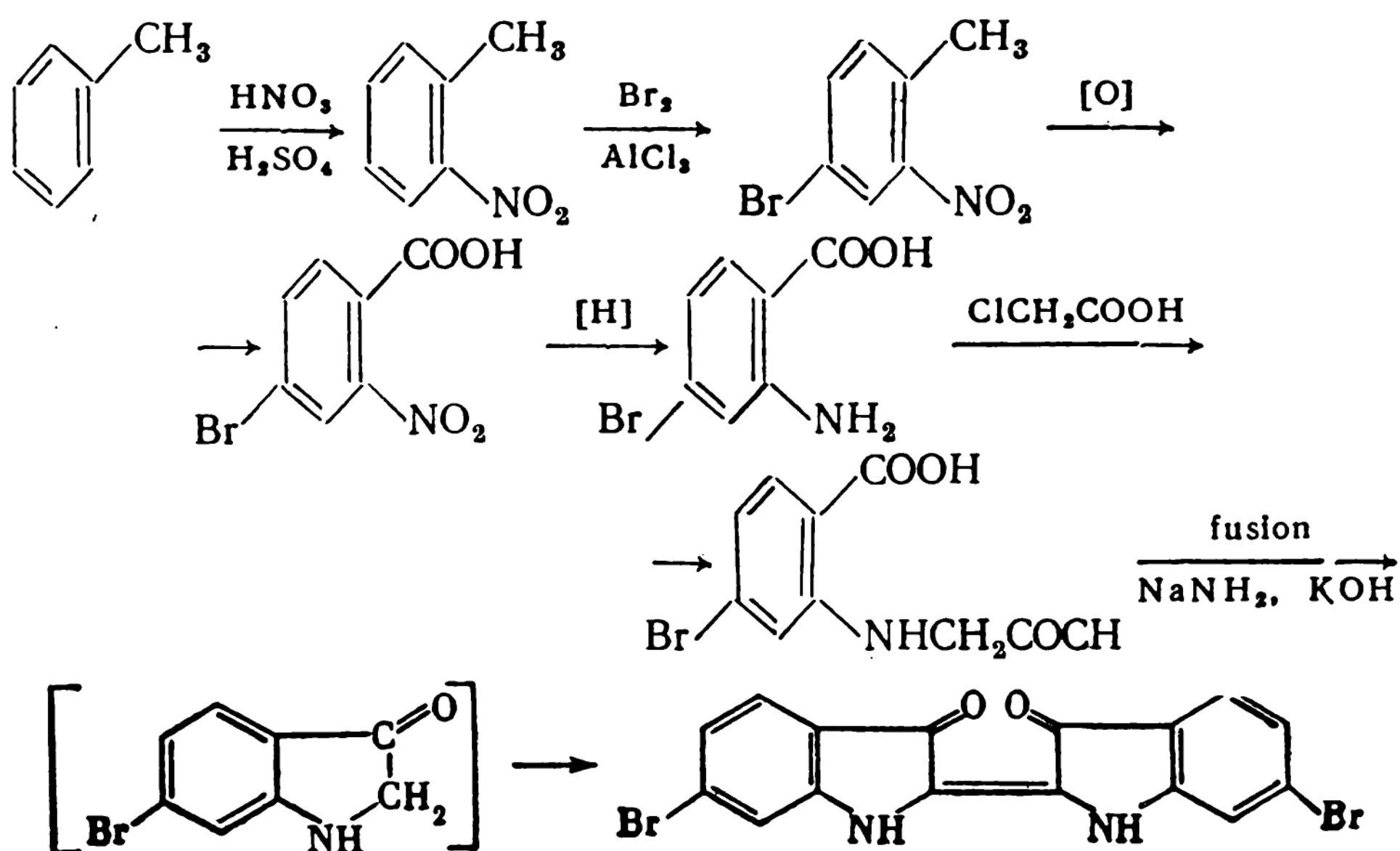


60. The preparation of indigo should be accomplished by using substituted anilines as starting materials:



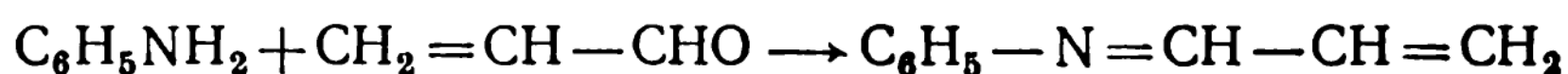
See also Problem 61.

61. 6,6-Dibromoindigo can conveniently be made from 4-bromoanthranilic acid:



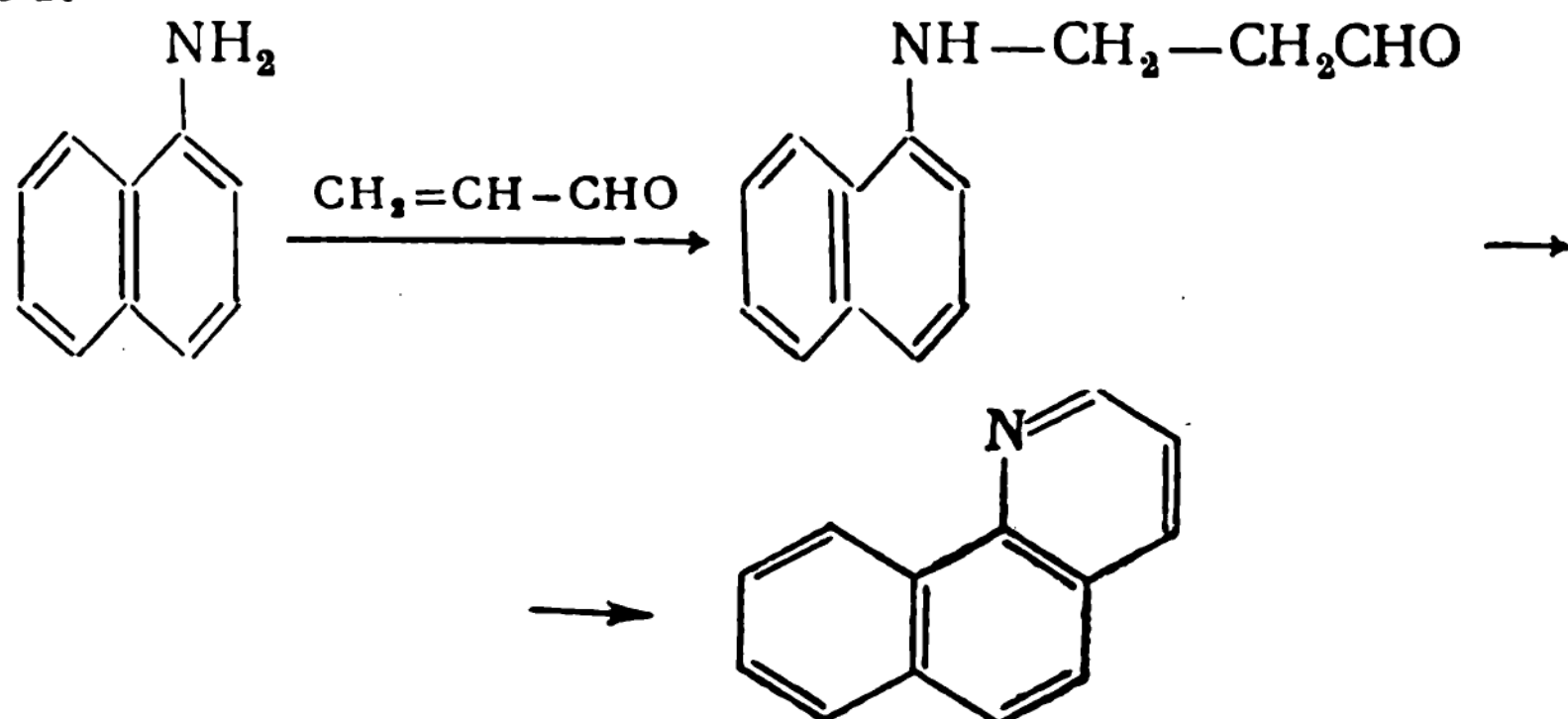
62. Use the Hantzsch method—the condensation of acetoacetic ester with acetaldehyde and ammonia.

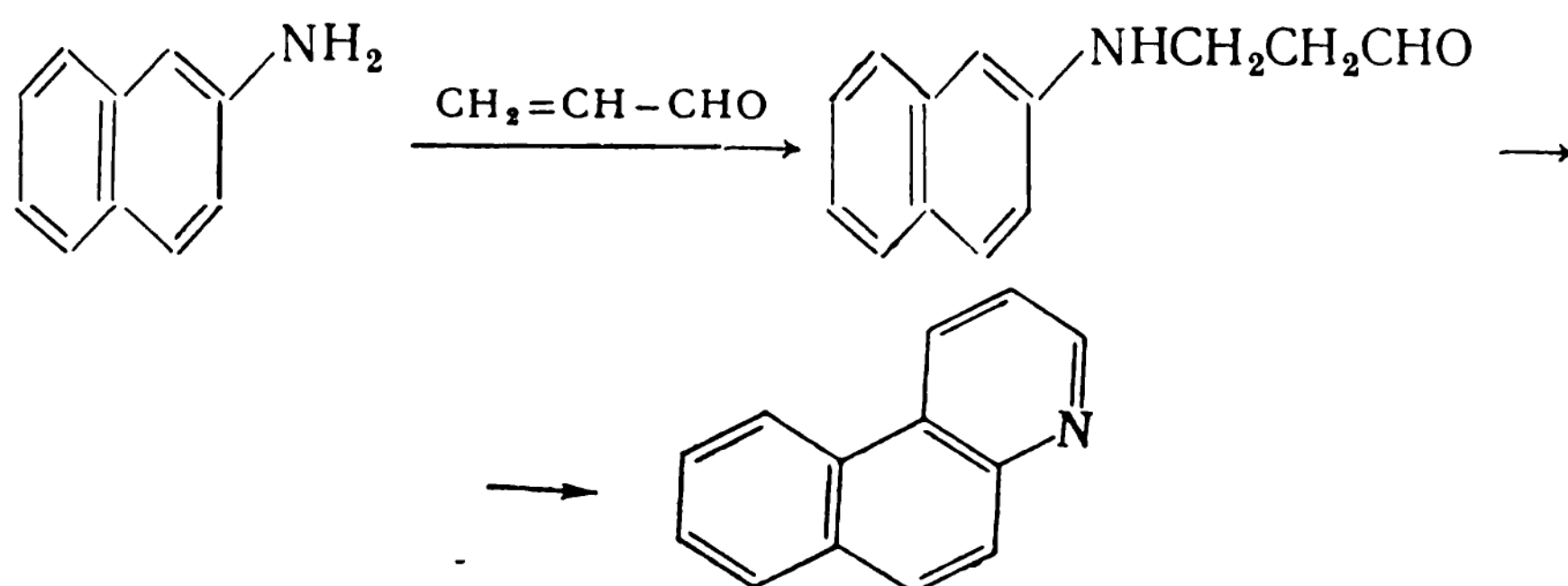
63. If the reaction proceeded according to the scheme B



then in the case of crotonaldehyde (the Doebner-Miller synthesis) it would have led first to the corresponding Schiff base and then to 4-methylquinoline. What is actually obtained is 2-methylquinoline, i.e., the reaction proceeds according to the scheme A.

64.

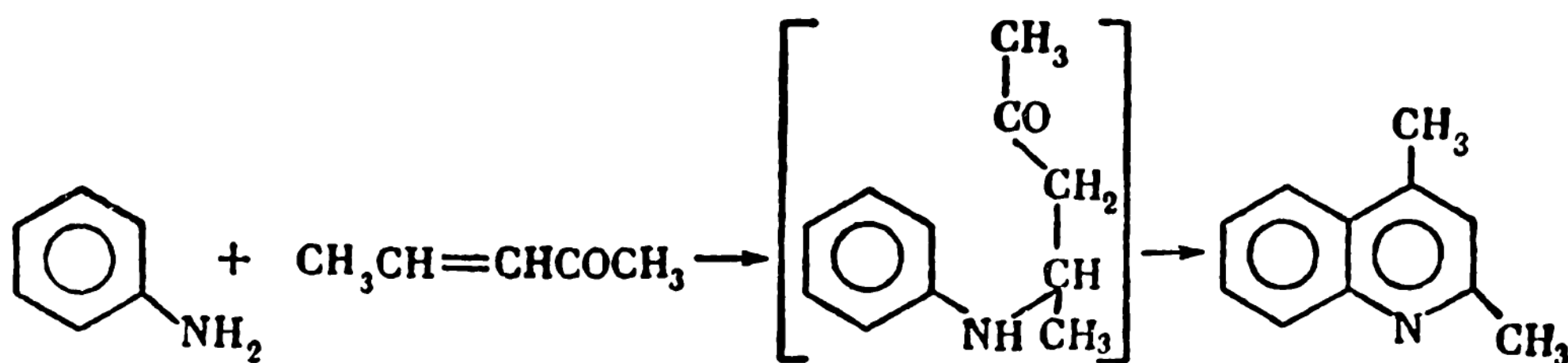




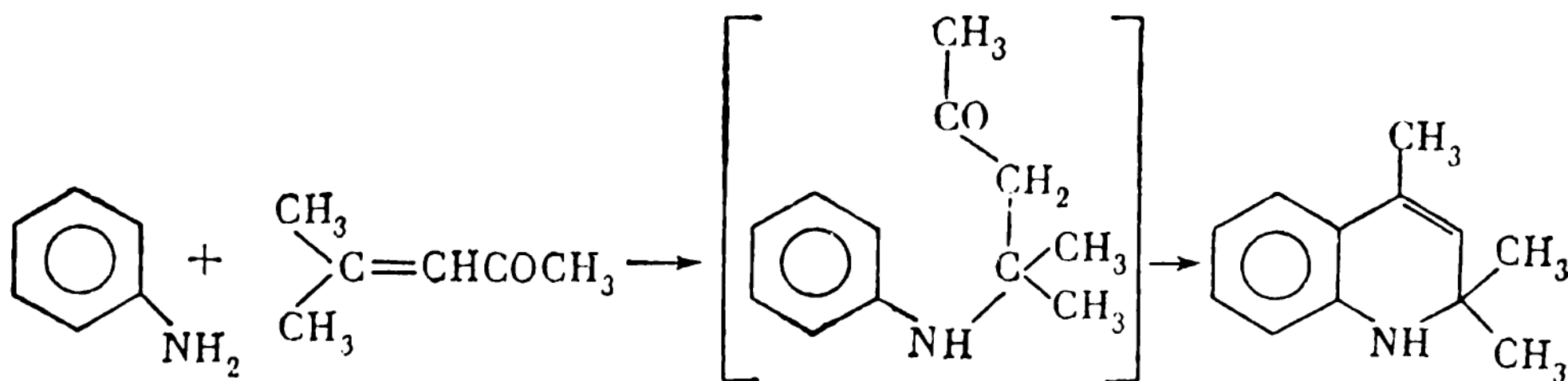
β -Naphthylamine will react more readily since in this case the cyclization, which is the second step of the reaction, will involve the most reactive α -position of the naphthalene nucleus.

65. (a) See Problem 67.

(b) The interaction of acetaldehyde with acetone gives a mixture of crotonaldehyde, mesityl oxide and ethylideneacetone. Under the conditions of the Doebner-Miller reaction crotonaldehyde gives quinaldine (see Problem 67), and ethylideneacetone gives 2,4-dimethylquinoline



Mesityl oxide will not undergo cyclization with the formation of a quinoline derivative:

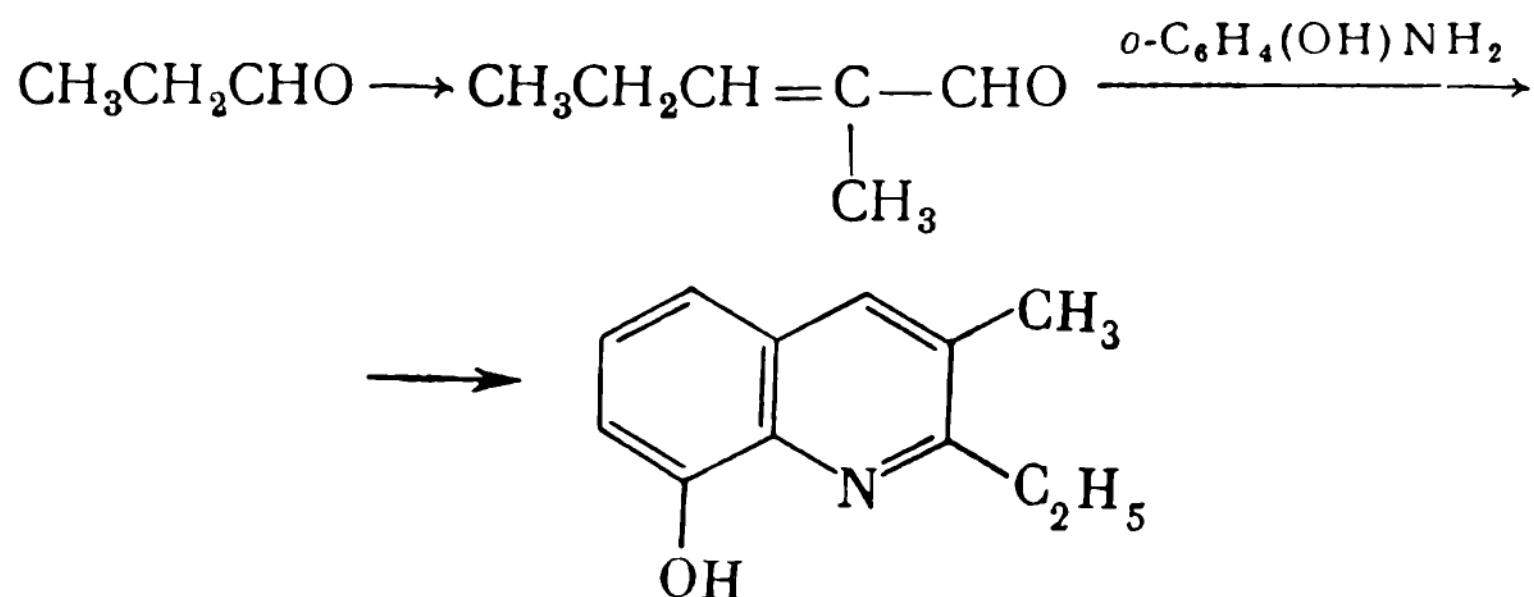


The resulting dihydroquinoline has a quaternary carbon atom, which renders it incapable of dehydrogenation.

66. The Doebner-Miller or Skraup syntheses should be used and the following starting materials taken: (a) *p*-anisidine

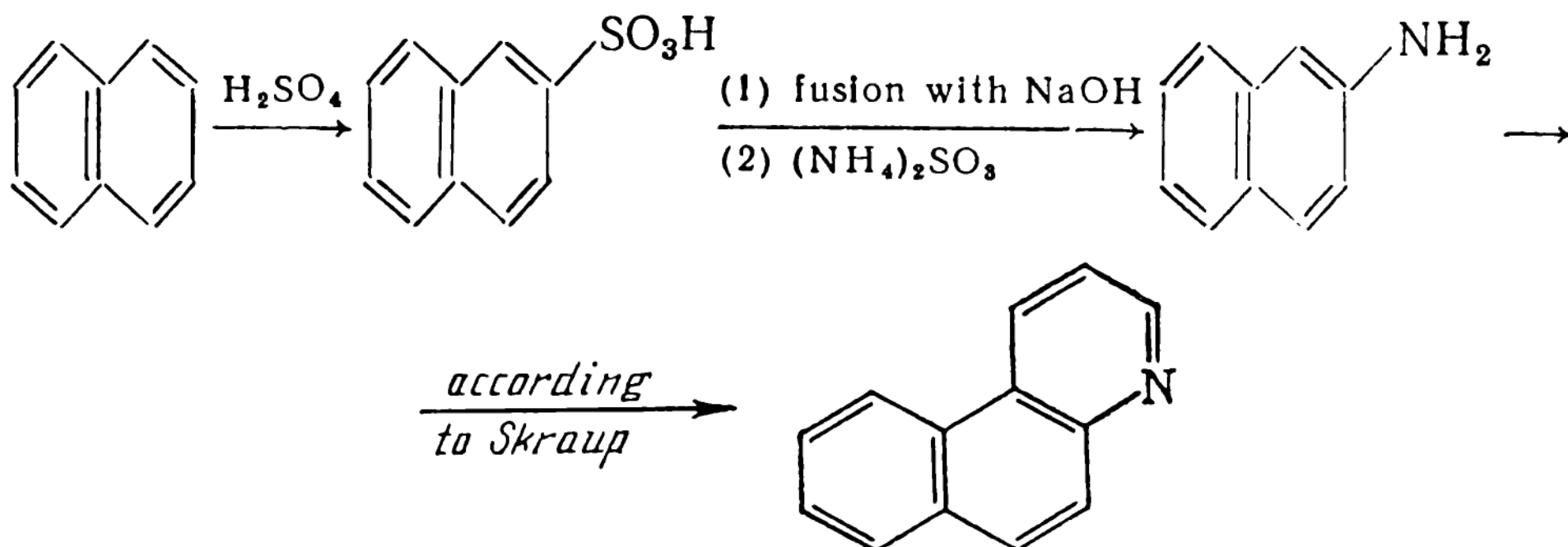
and methyl vinyl ketone; (b) 3,5-dimethyl-4-methoxyaniline and acrolein; (c) *p*-anisidine and acrolein; (d) *m*-chloroaniline and acetaldehyde (under the reaction conditions the latter changes into crotonaldehyde); (e) *o*-toluidine and acrolein; the subsequent bromination of the substituted quinoline obtained (the orienting effect of the methyl group in the benzene ring of quinoline) yields a mixture of bromo derivatives, from which there can be isolated 7-bromo-8-methylquinoline.

67. It can be made from *o*-aminophenol and propionaldehyde (the croton condensation into α -methyl- β -ethylacrolein) by the Doebner-Miller reaction

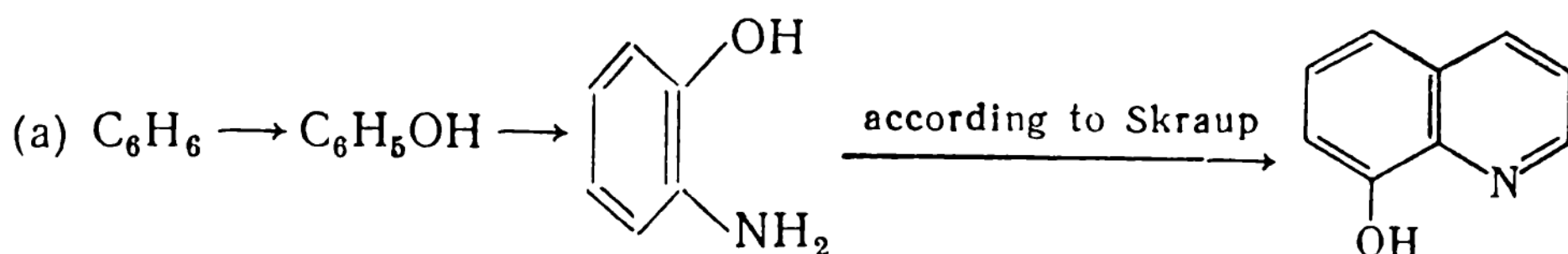


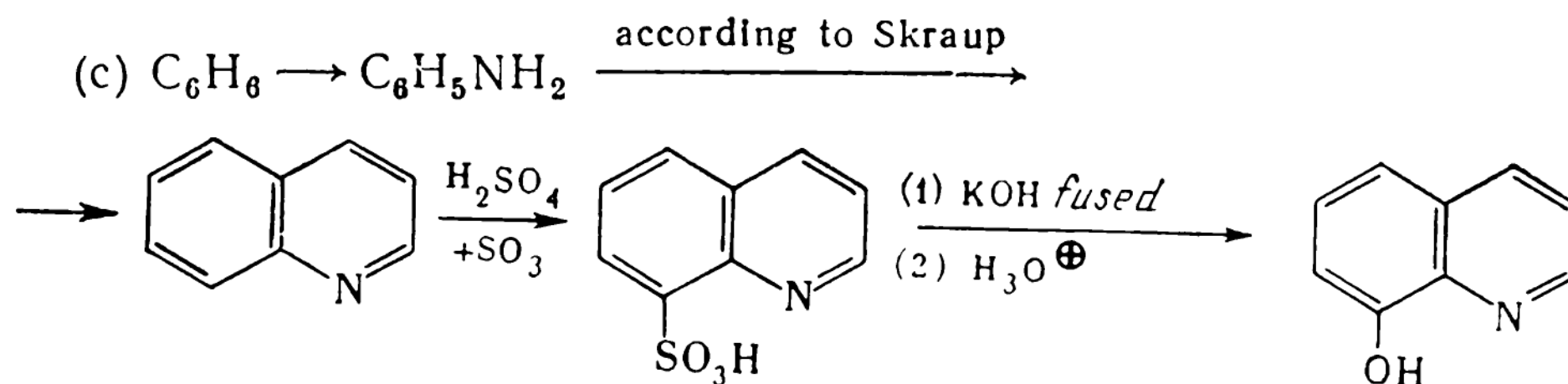
68. Use should be made of the Doebner-Miller or Skraup method as applied to cinnamaldehyde and *o*-toluidine.

69. See answer 64; β -naphthylamine is preferably made from naphthalene through the use of the Bucherer reaction:

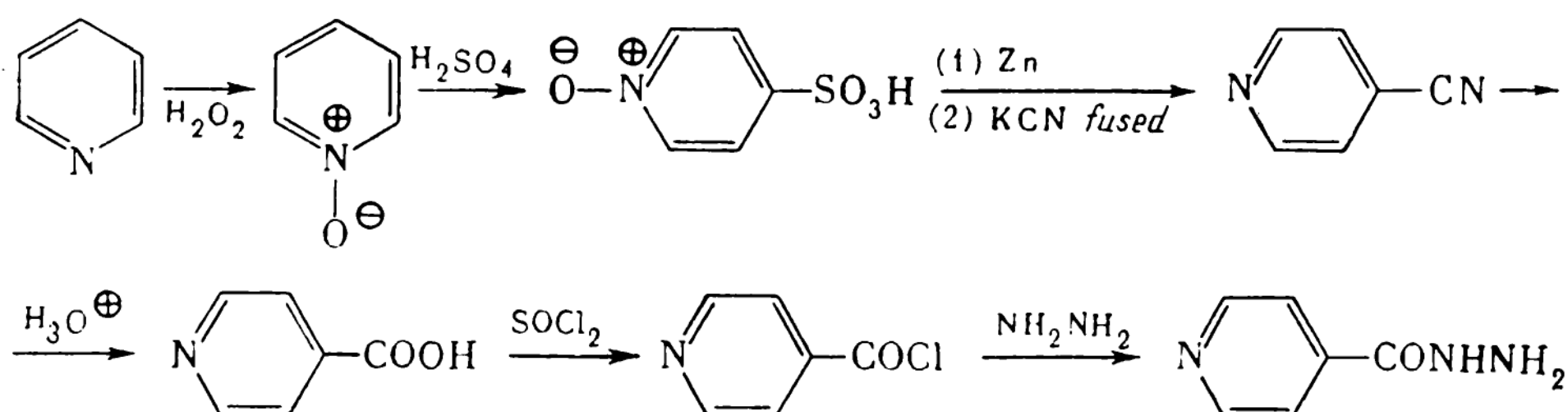


70. It can be made in two ways: either from *o*-aminophenol or from quinoline:





71. Advantage should be taken of the ease of substitution in pyridine N-oxide (see Problem 19):

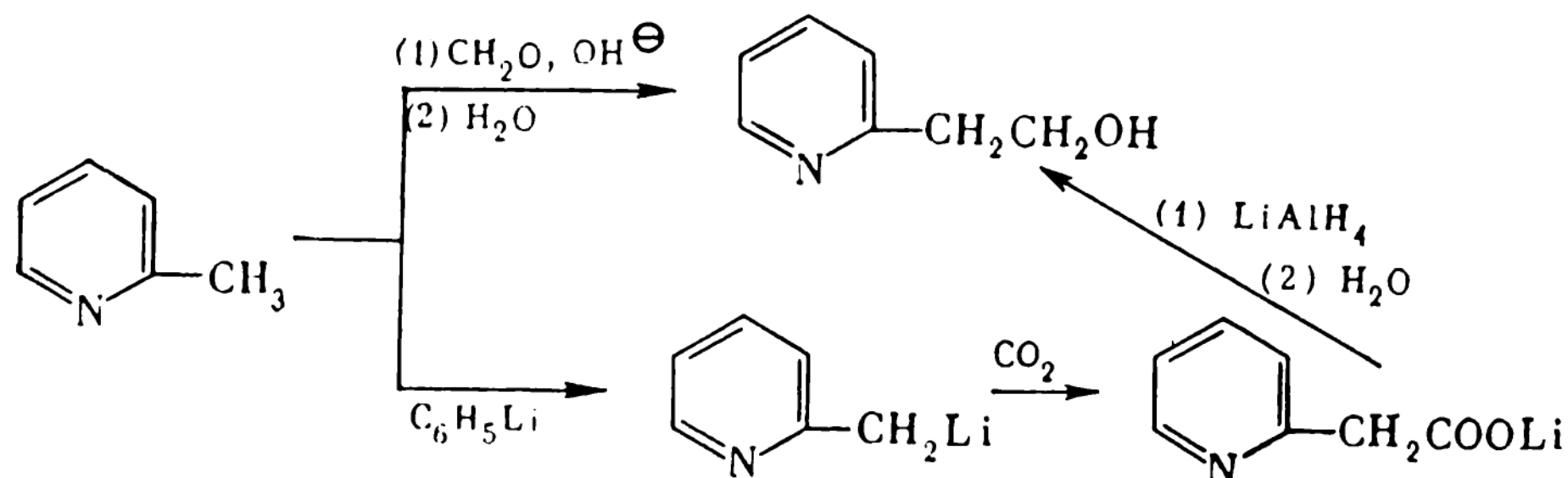


72. Use must be made of an ordinary electrophilic substitution in the pyridine nucleus: the sulphonation of pyridine leads to pyridine- β -sulphoacid, which together with NaCN gives β -cyanopyridine; the latter is converted upon saponification to nicotinamide.

73. Nicotinamide (see answer 72) is hydrolysed to the acid, which is converted to the acid chloride and use is then made of the action of diethylamine.

74. The alkylation of pyridine by the action of phenyllithium should be used and α -phenylpyridine oxidized (the benzene ring is more readily oxidizable than the pyridine ring).

75. Use should be made of the increased mobility of the CH bonds in the methyl group of methylpyridine (see Problems 22-25).



76. Quinaldine must be prepared (according to the Doebner-Miller mechanism) and the methyl group in it oxidized to the carboxylic group.

77. Quinoline is prepared and oxidized to quinolinic acid, which is allowed to react with ammonia to yield its imide; the potassium derivative of this imide is then alkylated with ethyl bromide.

78. First 8-hydroxyquinoline is prepared (Problem 70), and then the substitution is effected by iodine (in the presence of mercuric oxide) in the benzene ring activated by the OH group.

79. 8-Hydroxyquinoline (for its preparation see Problem 70) is sulphonated and then use is made of the action of potassium iodide and calcium hypochlorite mixture.

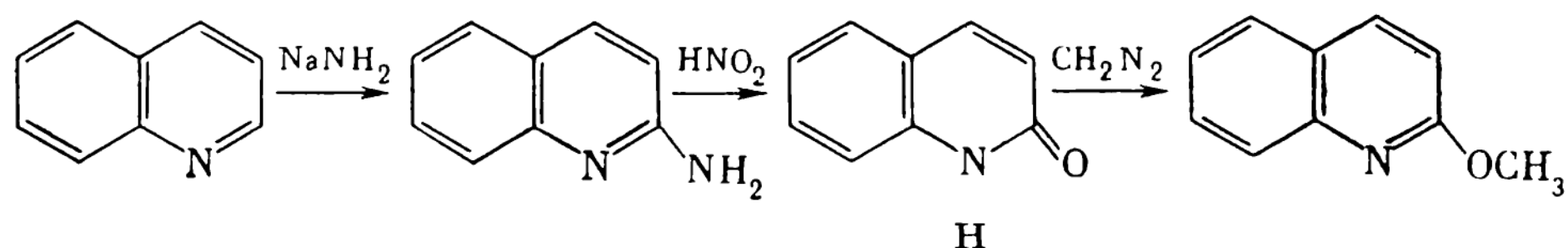
80. 8-Hydroxyquinoline (see Problem 70) is subjected to bromination.

81. See Problems 78-80.

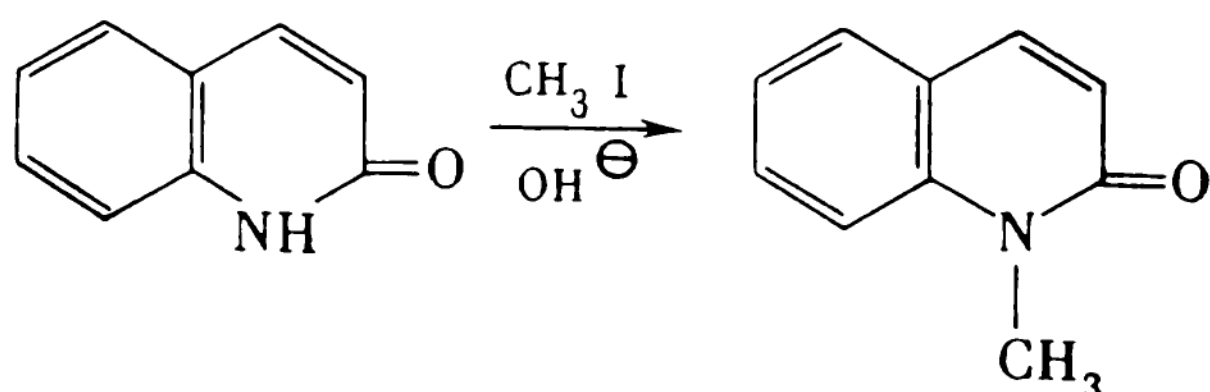
82. Use should be made of the substitution (azo coupling) in the activated phenol nucleus of 8-hydroxyquinoline (see Problems 78-80). Coupling will take place in the *p*-position relative to the OH group.

83. See Problem 82; instead of a diazo compound from aniline, use should be made of a diazonium salt prepared from sulphanilic acid.

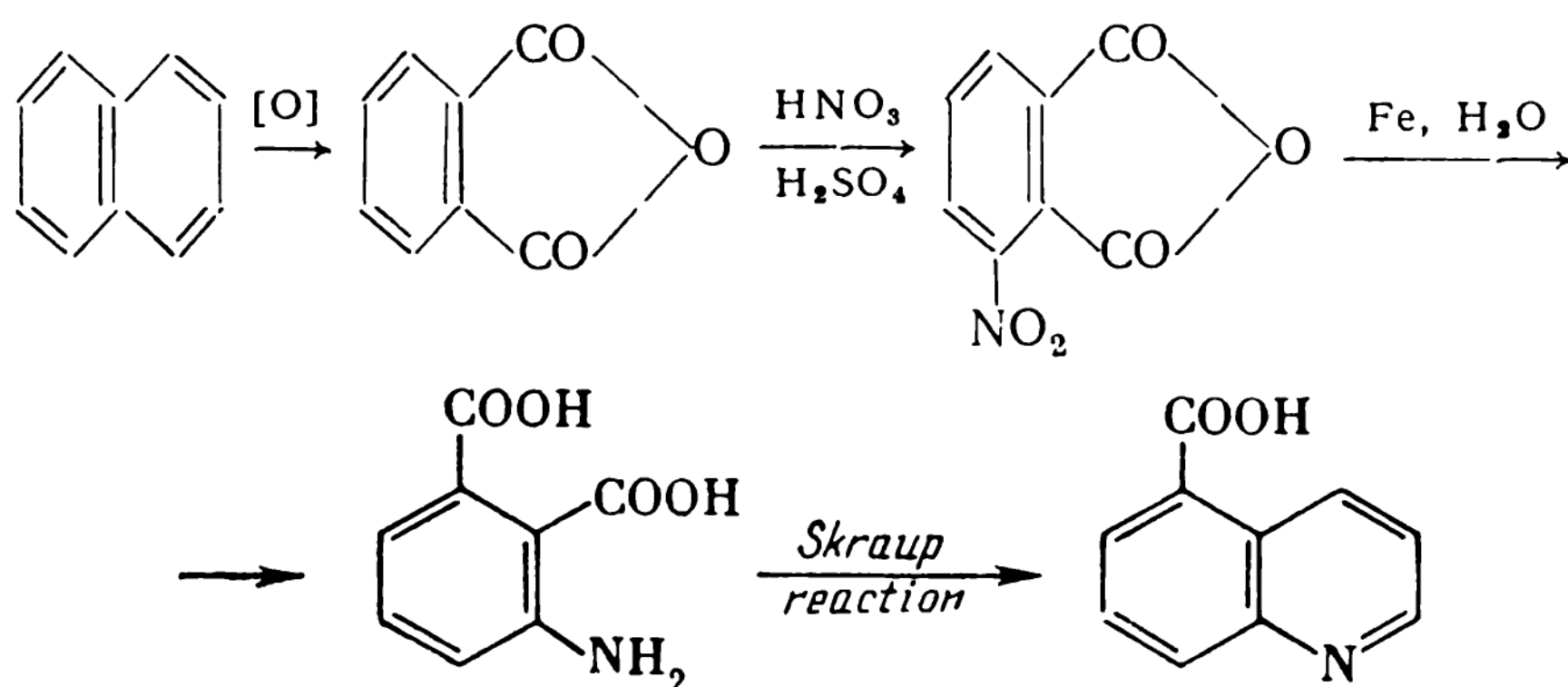
84. It would be most convenient to make use of the conversion of α -aminoquinoline to quinolone:



85. This problem is analogous to the previous one (84), except that at the last stage use is made of the action of methyl iodide:



86. Phthalic anhydride is prepared from naphthalene by oxidation (see Chapter 5). The nitration of phthalic anhydride gives 3-nitrophthalic acid (the 4-isomer thus obtained is more readily soluble in water and is separated upon recrystallization), which is reduced to 3-aminophthalic acid and then converted by the Skraup reaction to quinoline-5-carboxylic acid: this involves the elimination of one of the carboxylic groups:

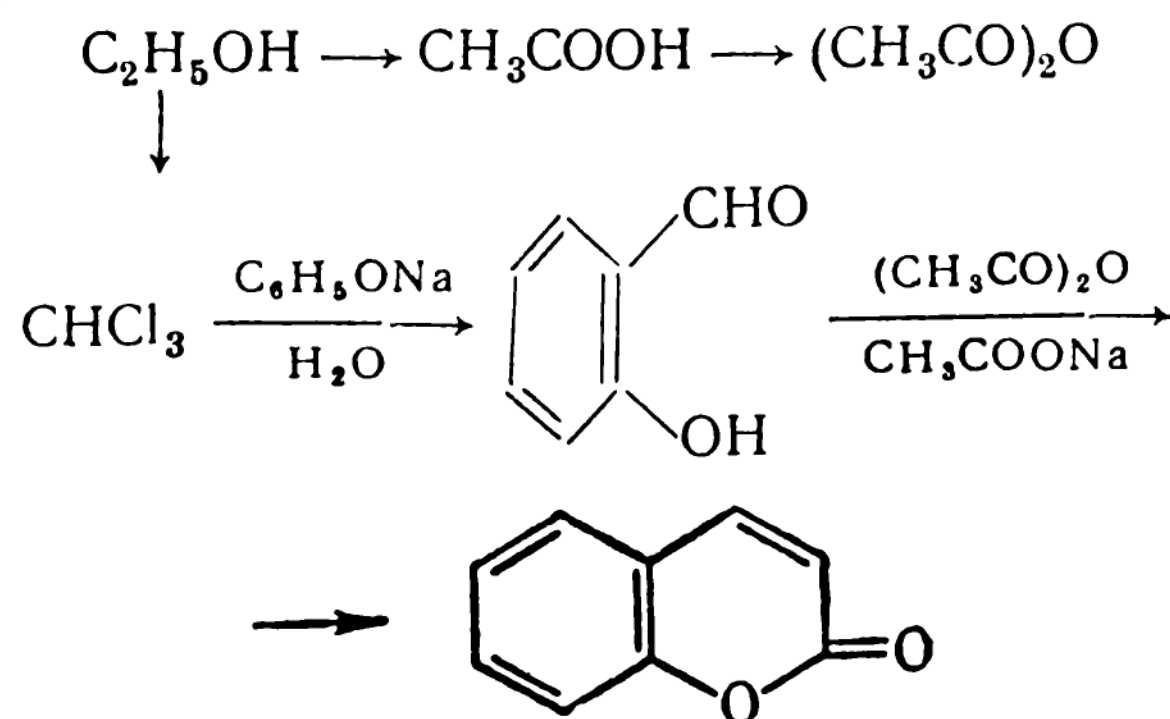


87. The hydroxy group is methylated and the resulting 5-methoxyquinoline is subjected to acylation by the Friedel-Crafts mechanism; then the acetyl group is reduced to an ethyl group and the compound obtained is demethylated by the action of hydrobromic acid on heating.

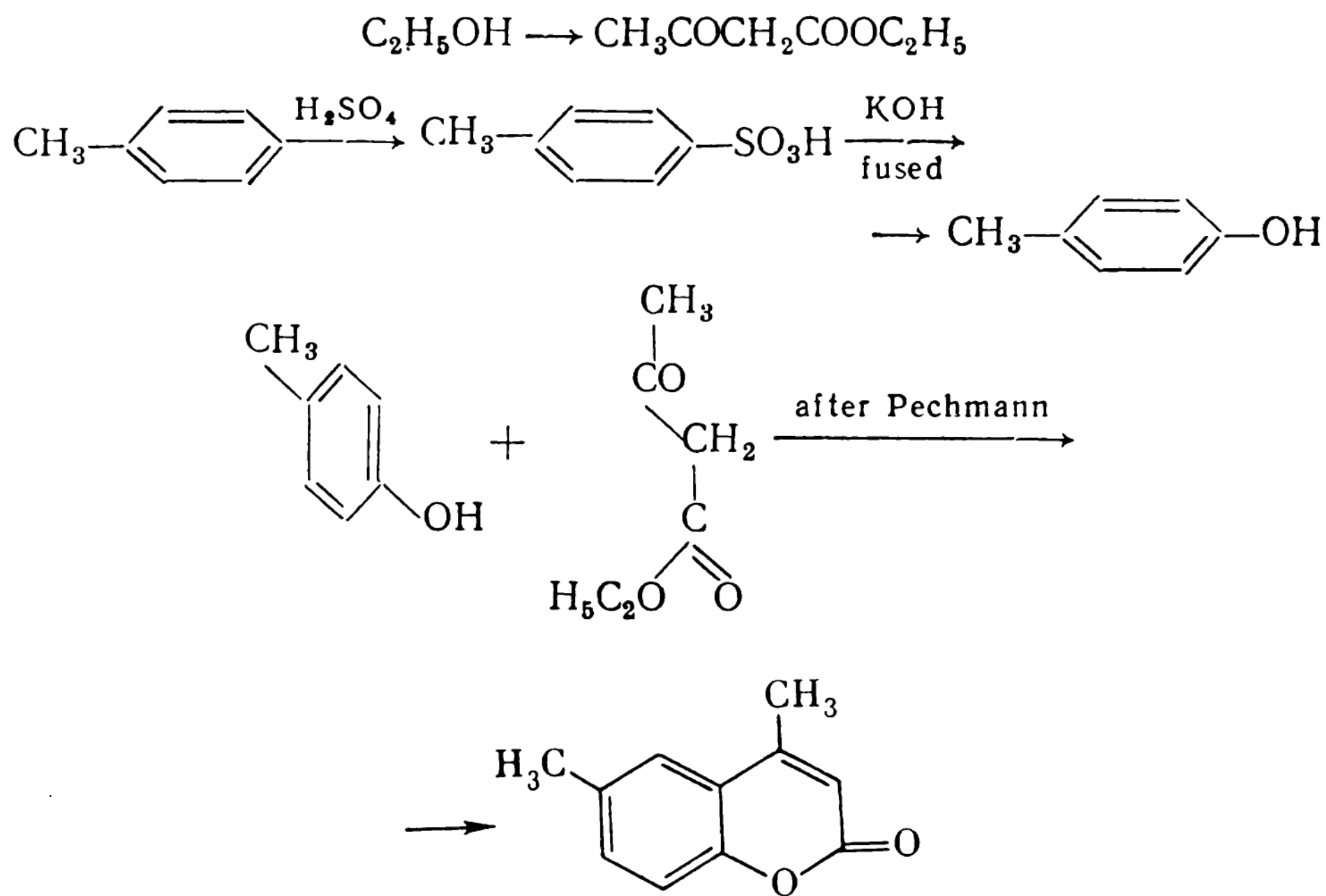
88. It is expedient to make use of 8-hydroxyquinoline (see Problem 70) and to accomplish conversions analogous to those in Problem 87.

89. Use is made of the action of phenyllithium on quinoline (see 74).

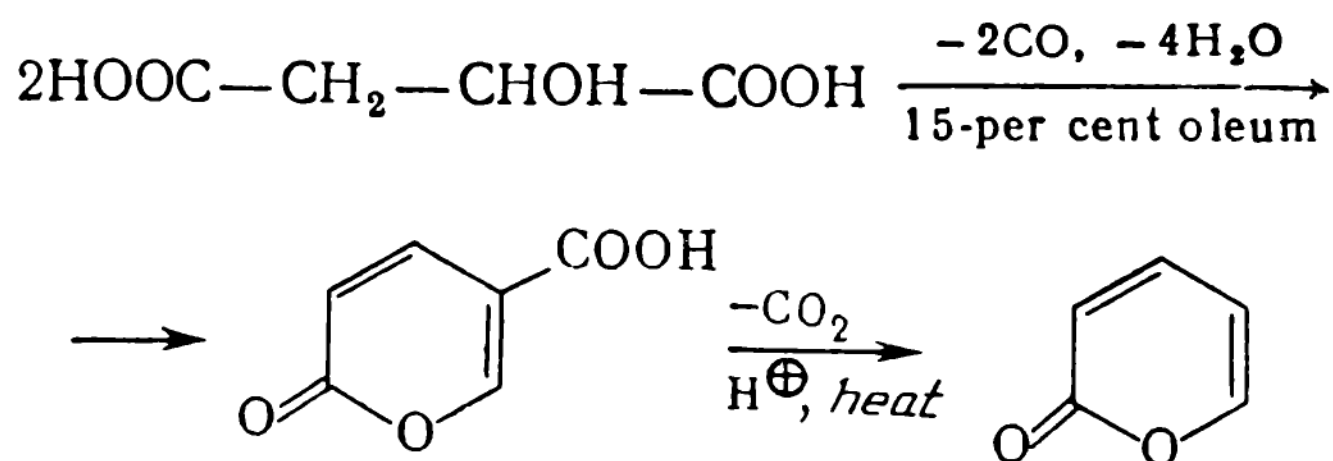
90. First acetic anhydride is prepared and then salicylic aldehyde by the Reimer-Tiemann reaction:



91. *p*-Cresol and acetoacetic ester should first be made:

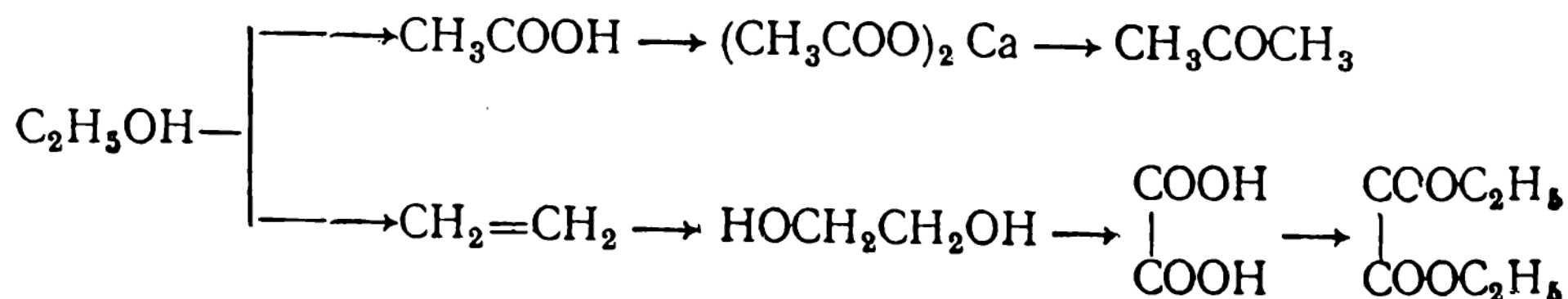


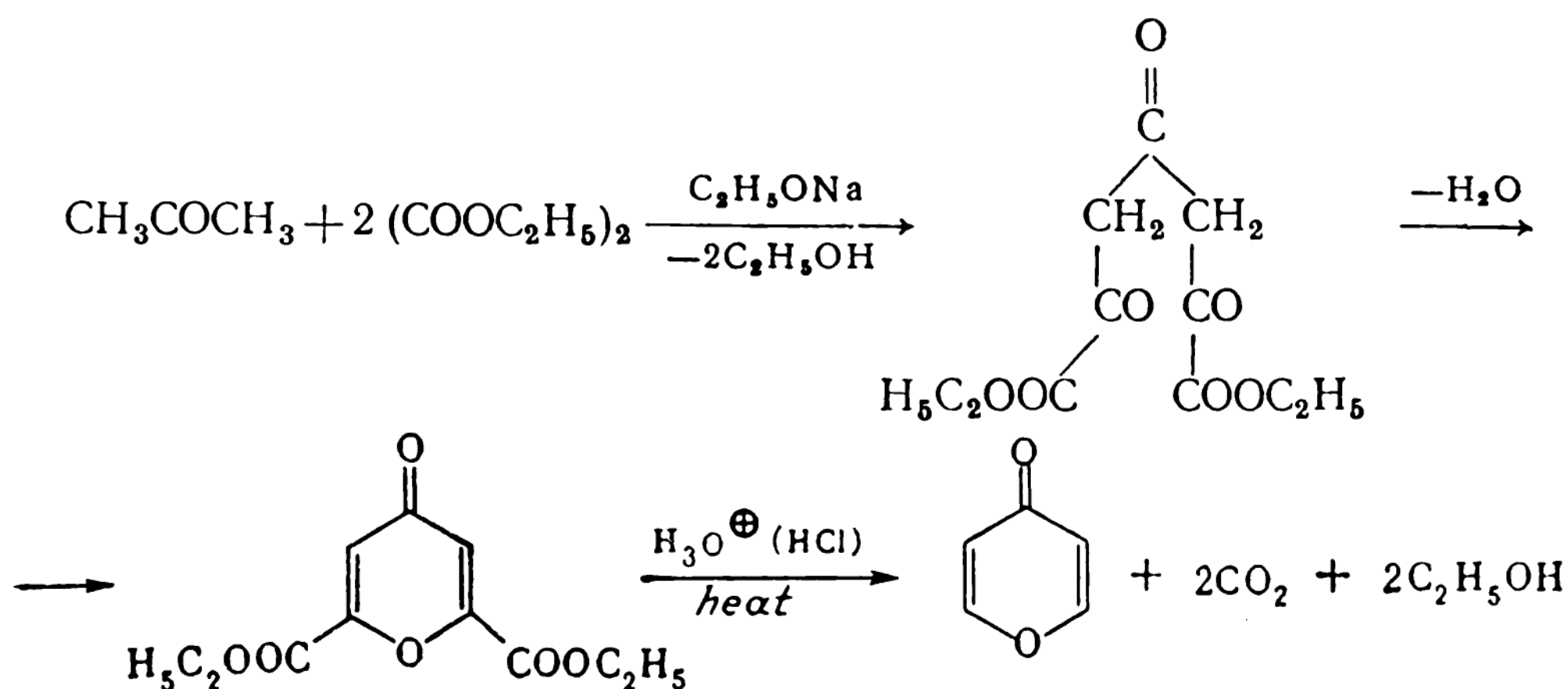
92. The classical method consists in the following: malic acid is acted on by 15-per cent oleum:



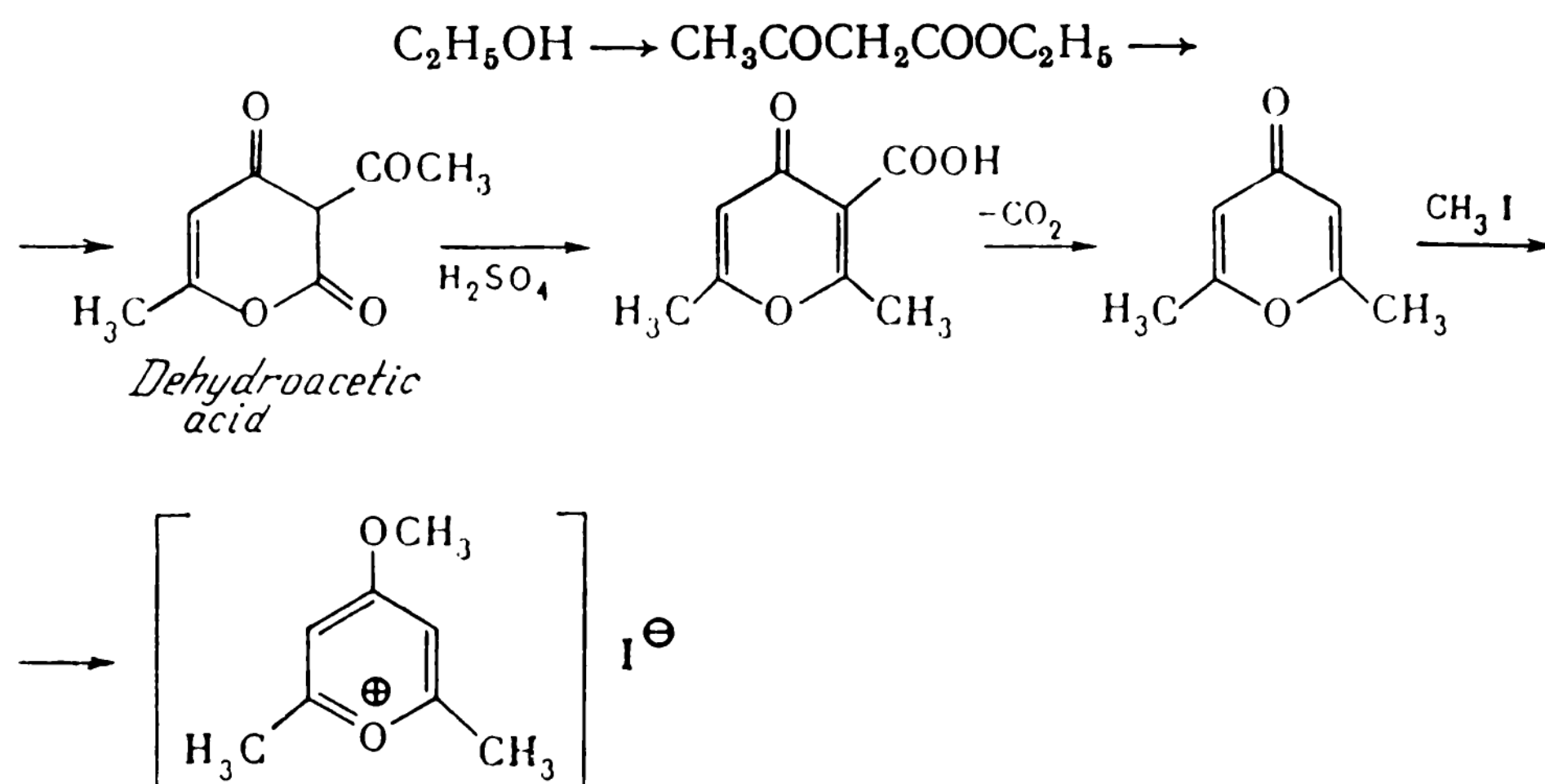
The conversion of ethanol to malic acid is accomplished via dibromoethane, succinic acid, and bromosuccinic acid.

93. Acetone and diethyloxalate should first be synthesized from ethyl alcohol:





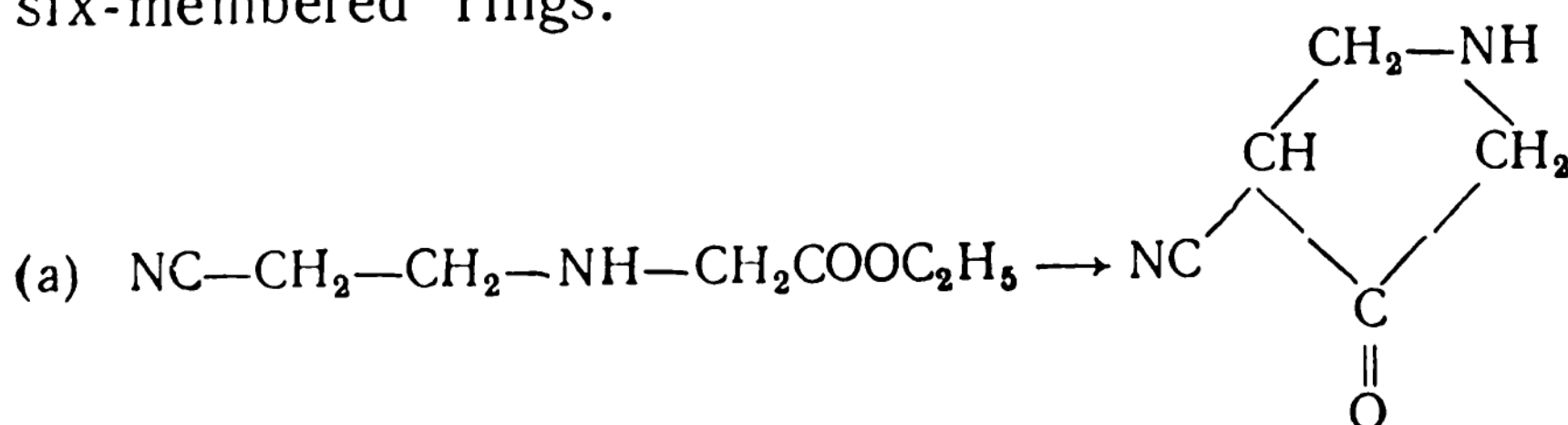
94. Dehydroacetic acid should first be prepared through condensation:

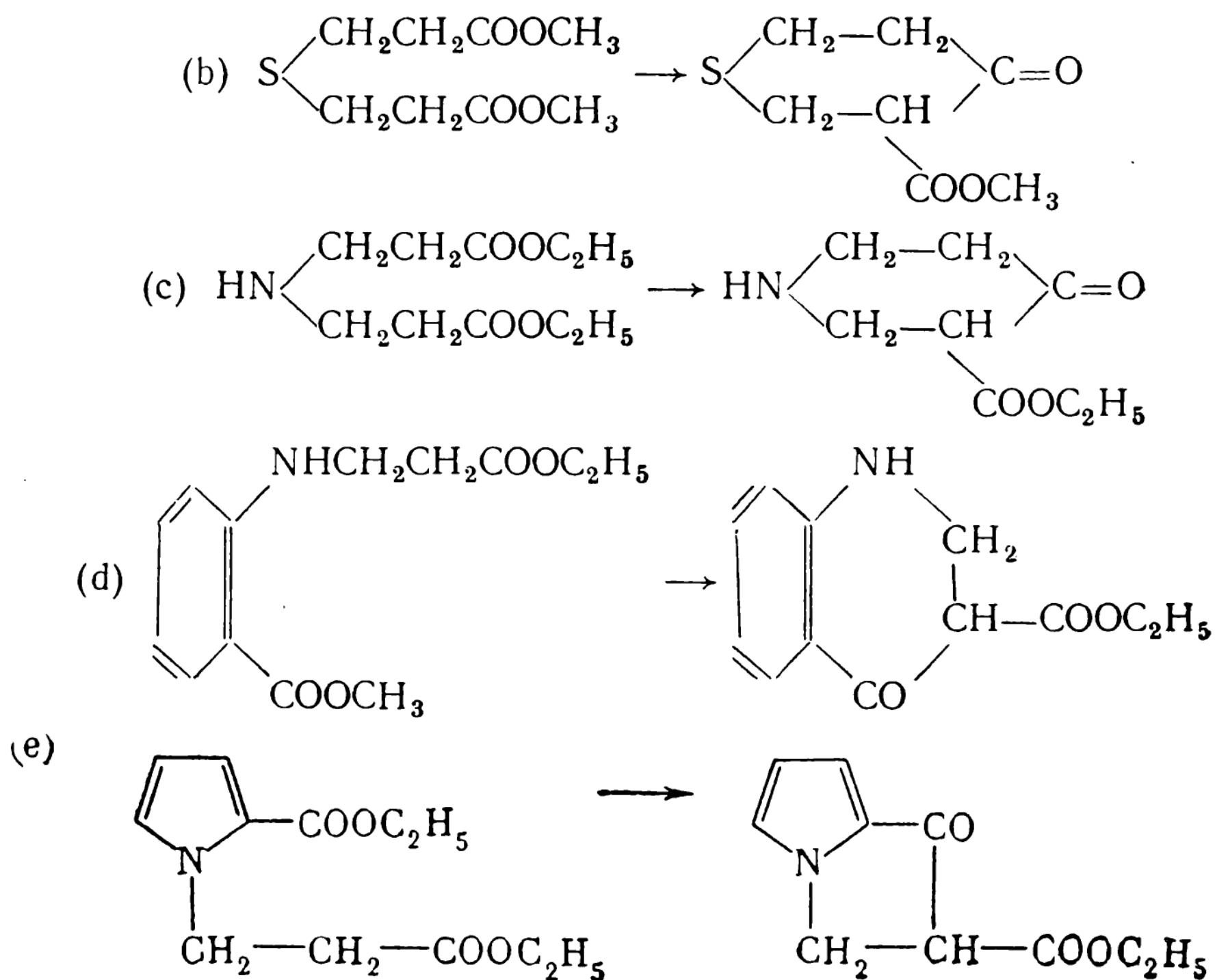


95. Tetrahydroquinoline and tetrahydroisoquinoline.

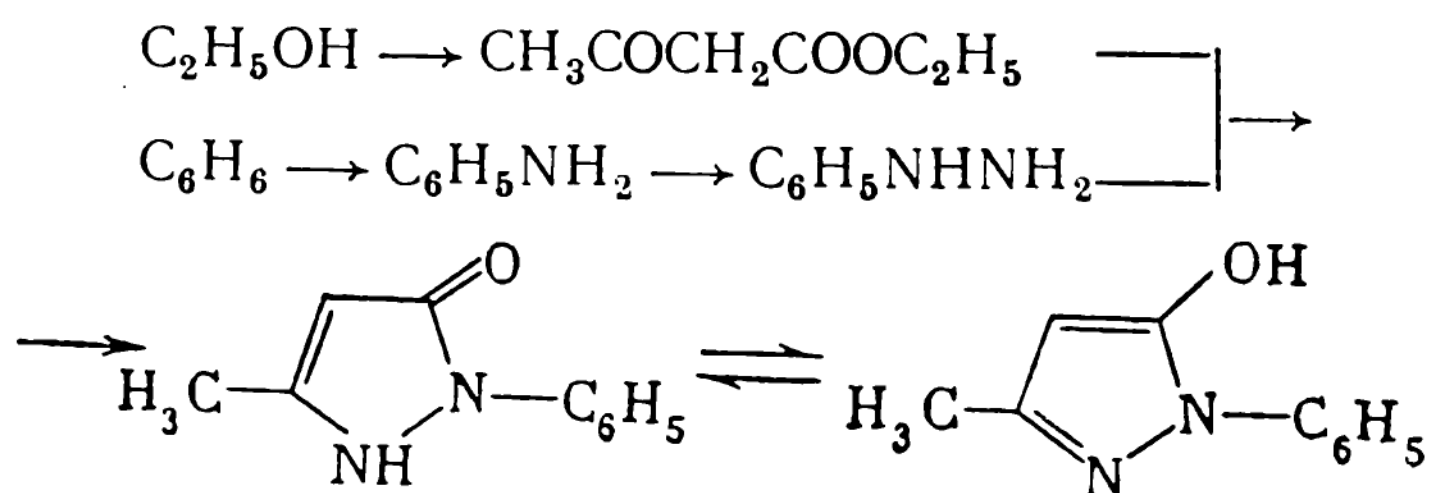
96. Oxazines, thiazines, phenazines, thiophenazines, quinoxalines, dioxans, thioxanes, etc.

97. The Dieckmann condensation, which is a variety of ester condensation, proceeds with the formation of five- and six-membered rings:



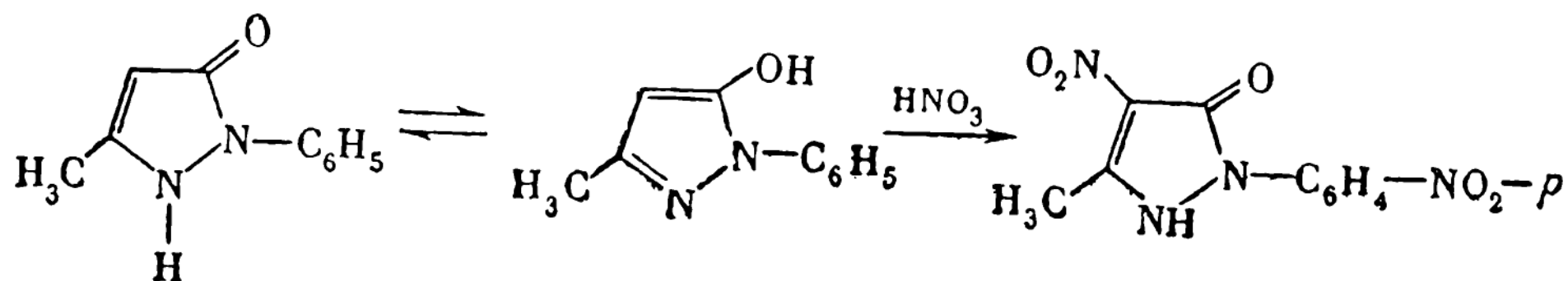


98. Use is made of the reaction of acetoacetic ester with phenylhydrazine:

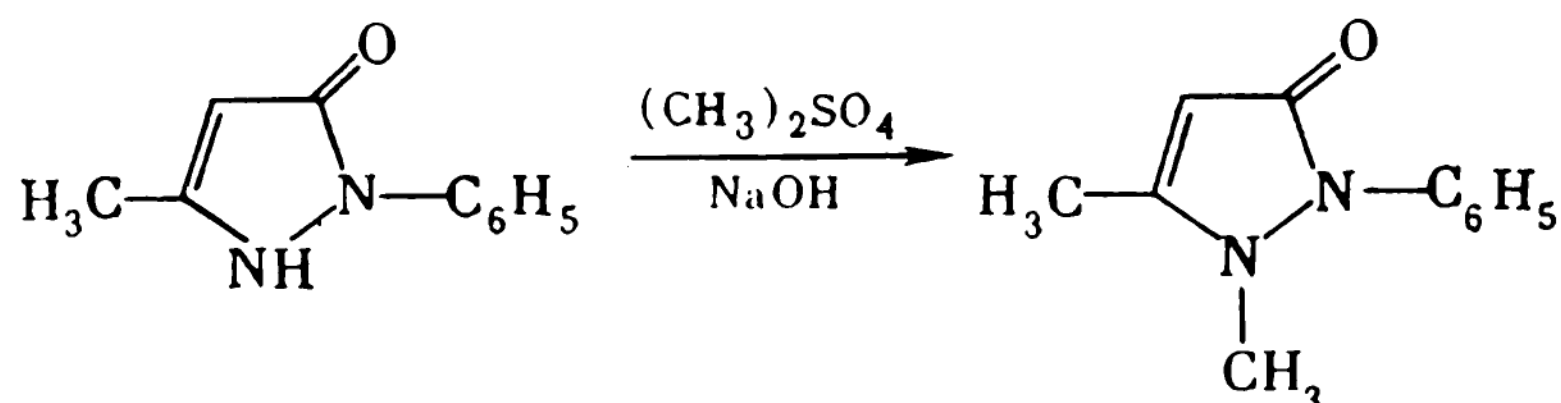


99. The solution of this problem is analogous to that of the previous one with the only difference that benzoylacetate should be used in this case as the starting material.

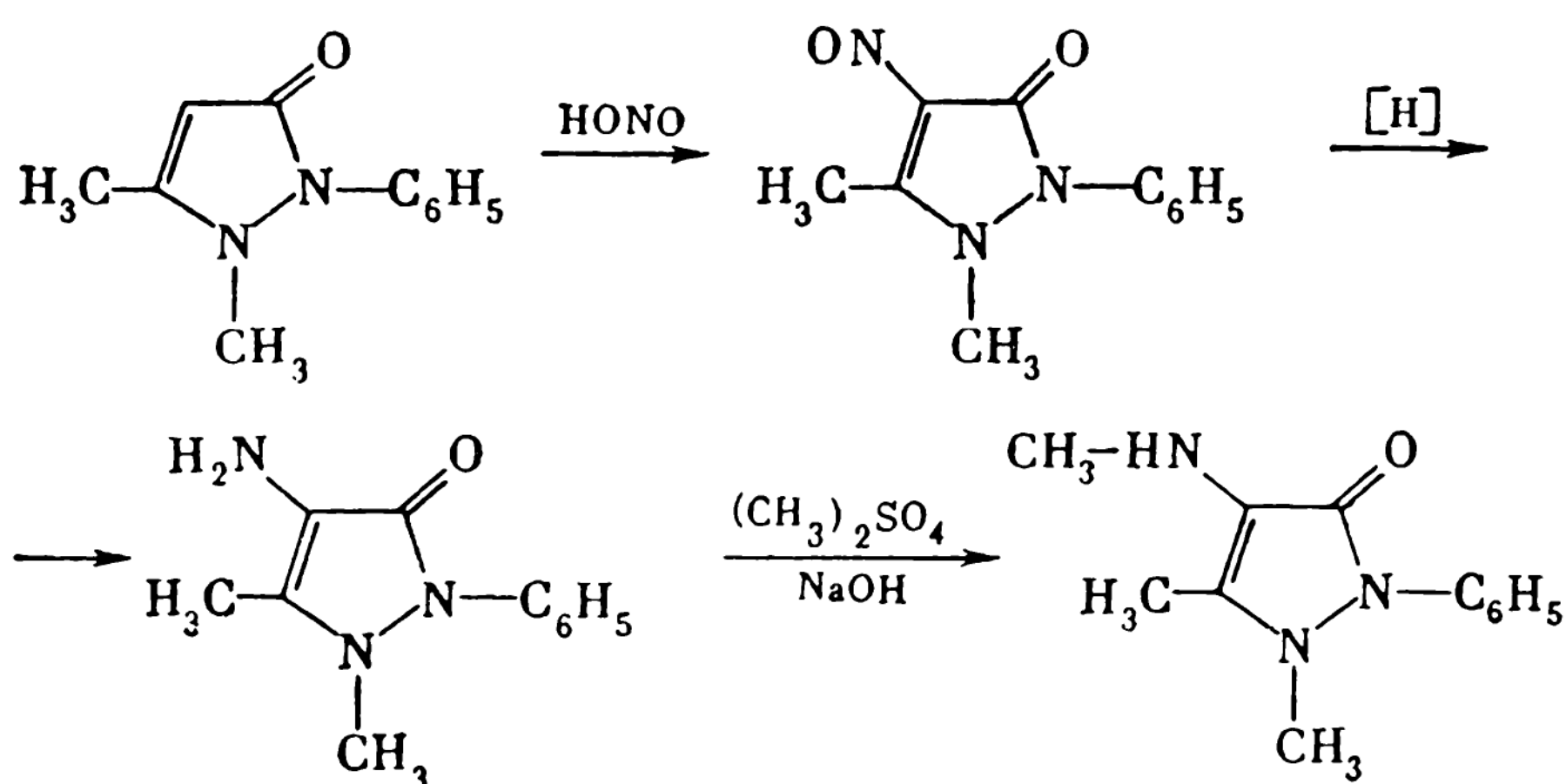
100. 3-Methyl-1-phenyl-5-pyrazolone (for its synthesis see Problem 98) is subjected to nitration:



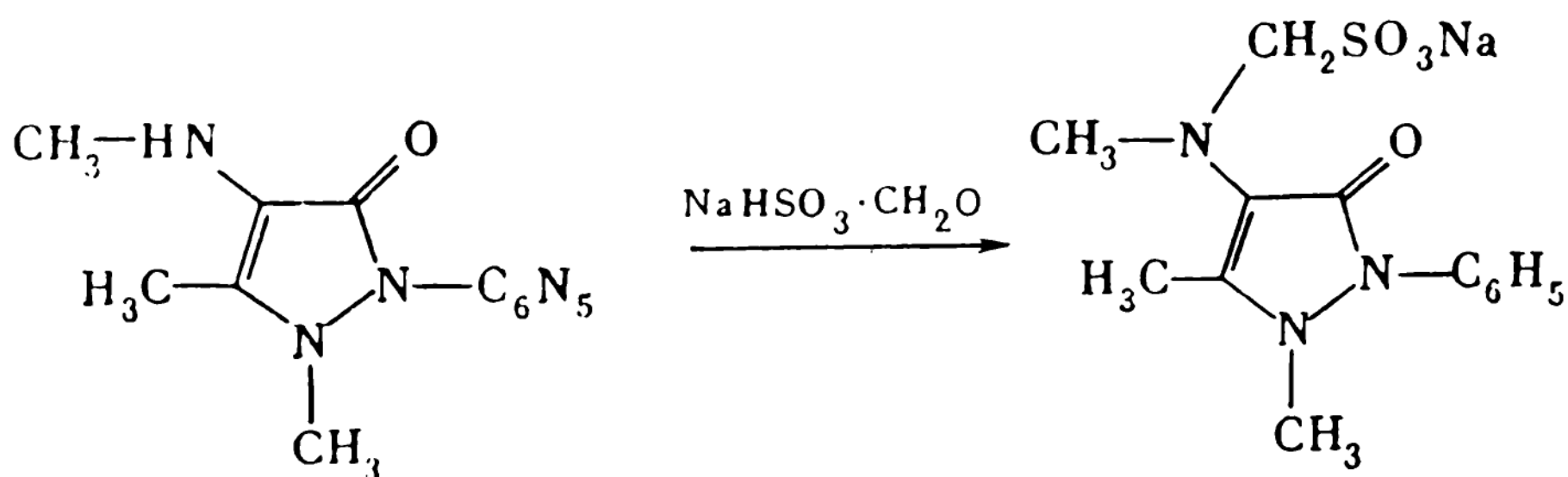
101. 3-Methyl-1-phenyl-5-pyrazolone (see 98) is subjected to alkylation:



102. 2,3-Dimethyl-1-phenyl-5-pyrazolone (for its synthesis see 101) is subjected to nitrosation; the nitro derivative obtained (nitrosoantipyrine) is reduced and alkylated:



103. Amidopyrine (see 102) is treated with rongalite (by addition of formaldehyde to sodium bisulphite) to give analgin:



TO THE READER

Mir Publishers would be grateful for your comments on the content, translation and design of this book. We would also be pleased to receive any other suggestions you may wish to make.

Our address is:

USSR, 129820, Moscow, I-110, GSP

Pervy Rizhsky Pereulok, 2

MIR PUBLISHERS

OTHER BOOKS FOR YOUR LIBRARY

FUNDAMENTALS OF ORGANIC CHEMISTRY

A.N. Nesmeyanov, Mem. USSR Acad. Sci., **N.A. Nesmeyanov**, D. Sc.

This is a four-volume textbook intended for systematic study of organic chemistry. The material is divided into two parts and covers a considerably wider field than the normal university treatment of the subject. Part One (the first three volumes) is constructed on "classical" lines. Part Two (volume IV) is intended for attentive reading rather than for close study.

The book may be used for self-study and for reading the course of organic chemistry at universities and chemical higher schools. It will undoubtedly be of interest to post-graduates, teachers and young scientists and engineers working in the field of organic chemistry.

Volume I (1976). Part One. The Subject of Organic Chemistry. The Historical Background. Separation and Purification Methods. Analysis of Organic Compounds. Classification of Organic Compounds. **Acyclic Compounds.** *Saturated Compounds.* Alkanes. Halogen Derivatives. The Chemical Reaction. Saturated Alcohols. Esters of Mineral Acids. Oxonium Compounds. Carbonyl Compounds. Polymers and Polymerization. Dialdehydes, Ketoaldehydes and Diketones. Carboxylic Acids and Their Functional Derivatives. Mesomerism. The Inductive Effect. Sulphur Compounds. Nitrogen Derivatives. Quantum-Chemical Treatment of the Electronic Structure of Molecules. *Unsaturated Compounds.* Olefins. Geometrical Isomerism I. Acetylenes. Dienes. Polyenes. Enynes. Polyynes. Rubbers. Halogen Derivatives. Alcohols. Acetylenic Alcohols and Ethers. Carbonyl Compounds. Unsaturated Acids. Vinylogy and the Tautomeric Effect of the Carbon-Carbon Double Bond. Stereochemistry. Geometrical Isomerism II. Physical Methods of Determination of Organic Structure I.

Volume II (1977). Heterofunctional Compounds. Aminoalcohols. Hydroxy Acids. Stereochemistry. Optical Isomerism I. Diastereoisomerism. Stereoregular Polymers. Aldehydic and Ketonic Acids. Tautomerism. Hydroxyaldehydes and Hydroxyketones. Carbohydrates. Stereochemistry of Monosaccharides. Optical Isomerism II. Alcoholic Fermentation and Cellular Respiration. Krebs Cycle. Synthesis of Sugars in Plants. Amino Acids. Dipeptides and Polypeptides. Imino and Nitrilic Acids. Aminoaldehydes and Aminoketones. Steric Hindrances and Conformational Analysis. **Alicyclic Compounds.** Nomenclature. Conformational Analysis. Isomerism. *Alicyclic Hydrocarbons and Their Derivatives.* Small Rings. Five- and Six-Membered Rings. Interconversion of Rings. Alicyclic Compounds with Two or More Rings. Stereochemistry. Medium and Large Rings.

Valence Isomerism and Tautomerism. The Transannular Effect. Polycyclic Compounds. Physical Methods of Determination of Organic Structure II.

Volume III (1977). **Aromatic Compounds.** *Benzene and Its Derivatives.* Benzene and Its Structure. Physical Methods of Determination of Organic Structure III. Orientation in the Benzene Ring. Orientation in Nucleophilic Aromatic Substitution. Halogen Derivatives. Dehydrobenzene. Sulphonic Acids. Nitro Compounds. Amines. Diazo Compounds. Phenols. Charge-Transfer Complexes. Clathrates of Hydroquinone. Atropisomerism. Alcohols. Phenolic Alcohols. Aldehydes and Ketones. Quinones. Quinhydrone and Semiquinone. Carboxylic Acids. Phenolic Acids. Amino Acids. **Polycyclic Aromatic Compounds.** Compounds with Isolated Benzene Rings. Atropisomerism II. Condensed Aromatic Systems. Acenaphthene, Indene, Fluorene. Anthracene and Its Derivatives. Phenanthrene. Higher Condensed Hydrocarbons. **Heterocyclic Compounds.** *Five-Membered Compounds.* Rings with One Heteroatom. Five-Membered Heterocycles with Several Identical Heteroatoms. Five-Membered Heterocycles with Two Different Heteroatoms. *Six-Membered Heterocyclic Compounds.* Heterocycles with One Nitrogen Atom. Six-Membered Heterocycles with Two Nitrogen Atoms (Diazines). Six-Membered Heterocycles with Three Nitrogen Atoms. Nitrogen Bicyclic Heterocycles. Six-Membered Heterocycles with an Oxygen Atom. Six-Membered Heterocycles with Two Different Heteroatoms.

Volume IV (1978) **Part Two.** Organoelement Compounds, Nonbenzenoid Aromatic Systems. Carbanions, Free Radicals. Carbenes. Carbonium Ions. Elimination Reactions. Isoprenoids. Alkaloids of the Heterocyclic Series. Proteins, Nucleotides and Polynucleotides. Enzymes.

